JUL 15 1925
Medical Lib.

VOLUME 36 NUMBER 1

ARCHIVES
OF
INTERNAL MEDICINE

EDITORIAL BOARD
JOSEPH L. MILLER, Chicago
RICHARD C. CABOT, Boston LOUIS V. HAMMAN, Baltimore
GEORGE BLUE, Pasadena, Cal. WARFIELD T. LONGCOPE, Baltimore
M. B. THAYER, Baltimore

JULY 15, 1925

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $10.

Entered as Second-Class Matter, October 21, 1908, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

CONTENTS OF PREVIOUS NUMBERS

APRIL, 1933. NUMBER 4

Further Observations on the Use of a High Fat Diet in the Treatment of Diabetes Mellitus. L. H. Newburgh, M.D., and Phil L. Marsh, M.D., Ann Arbor, Mich.

A Stone-Statues Indice. H. Gray, M.D., Boston.

Albuminuria: Its Clinical Significance as Shown by Chemical Study of the Blood. T. Homer Coffen, M.D., Portland, Ore.

Clinical Experience with Quinidine. C. Sidney Burwell, M.D., and Francis R. Dieuaide, M.D., Baltimore.

Mycotic (Bacterial) Aneurysms of Intracranial Origin. Alfred Stengel, M.D., and C. C. Wolferth, M.D., Philadelphia.

Distribution of Sugar in Whole Blood, Plasma and Corpuscles; Permeability of Red Blood Corpuscles for Sugar in Diabetic and Non-diabetic Cases. Henry J. John, M.D., Cleveland.

A Study of Blood Pressure in Relation to Types of Bodily Habitus. Joseph W. Lautmann, M.D., St. Louis.

Hypercalcinemia in Hemolytic Jaundice. Herbert Z. Giffin, M.D., Rochester, Minn.

The Relation of Age and Obesity to Vital Capacity. Byron S. Brown, M.D., with the Assistance of Dorothy L. Flint, Buffalo, N. Y.

Acid-Base Equilibrium. I. Clinical Studies in Alkalosis. Alfred E. Bender, Madison, Wis.

Physical and Chemical Studies of Human Blood Serum. I. Study of Normal Subjects. Dana W. Atchley, Robert P. Loeb, Ethel M. Benedict and Walter W. Palmer, New York.

Physical and Chemical Studies of Human Blood Serum. II. A Study of Twenty-Nine Cases of Nephritis. Dana W. Atchley, Robert P. Loeb, Ethel M. Benedict and Walter W. Palmer, New York.

Physical and Chemical Studies of Human Blood Serum. III. A Study of Miscellaneous Disease Conditions. Dana W. Atchley, Robert P. Loeb, Ethel M. Benedict and Walter W. Palmer, New York.

Book Review.

MAY, 1933. NUMBER 5

Observations on the Value of Phenolsulfonphthalein in Estimating Liver Function. George Morris Piersol, M.D., and H. L. Bockus, M.D., Philadelphia.

The Heart in Diphtheria: A Clinical and Pathologic Study. Meinhard Loth, M.D., New Haven, Conn.

The Production of Atherosclerosis in Rabbits by Feeding Diets Rich in Meat. L. H. Newburgh, M.D., and Sarah Clarkson, M.S., Ann Arbor, Mich.

The Presence of Auer Bodies in Leukemic Tissues. Maurice N. Richter, M.D., New York.

Uricacidemia: Based on a Study of 1,500 Blood Chemical Analyses. Henry M. Feinblatt, M.D., Brooklyn.

The Effect of Splenectomy on the Hemopoietic System of Macacus Rhesus. E. B. Krumbhaar, M.D., and J. H. Musser, Jr., M.D., Philadelphia.

Thoracoplastic Compression of the Lung in Pulmonary Tuberculosis. Philip King Brown, M.D., and Leo Eloesser, M.D., San Francisco.

Constitutive Studies in Syphilis from a Clinical and Biologic Point of View. II. Normal Arsenic. John A. Fordyce, M.D.; Isadore Rosen, M.D., and C. N. Myers, Ph.D., New York.

Accurate Criteria for Differentiating Anemias. Russell L. Haden, M.D., Kansas City, Kan.

Book Reviews.

JUNE, 1933. NUMBER 6

The Clinical Significance of Albuminuria in Urine Volumes. T. Addis, M.D., San Francisco.

Studies on the Physiology of the Liver. IV. The Effect of Total Removal of the Liver After Pancreatectomy on the Blood Sugar Level. Frank C. Mann, M.D., and Thomas B. Magath, M.D., Rochester, Minn.

The Production of Urinary Calculi by the Devitalization and Infection of Teeth in Dogs with Streptococci from Cases of Nephrolithiasis. Edward C. Rosenow, M.D., and John G. Meisser, D.D.S., Rochester, Minn.

A Study of Macroscopic Fat in the Human Blood with Special Reference to Their Presence in Two Cases of Subacute Bacterial Endocarditis. John J. Sampson, M.D., William J. Kerr, M.D., and Miriam E. Simpson, Ph.D., San Francisco.

Primary Carcinoma of the Thymus. Victor C. Jacobson, M.D., Albany, N. Y.

Hydrogen-Ion Studies. VII. Experimental Nephritis in Rabbits with Monobasic Sodium Phosphate. Edwin F. Hirsch, M.D., Chicago.

The Dilatation of the Pulmonic Area of the Heart and Its Significance. James A. Hessell, M.D., Boston.

Stokes-Adams' Disease Due to Gumma of the Heart. Ralph H. Major, M.D., Kansas City, Kan.

Observations on the Blood Gases in Auricular Fibrillation and After the Restoration of the Normal Mechanism. Harold J. Stewart, M.D., Baltimore.

Experimental Uranium Nephritis: A Chemical and Pathologic Study. Franklin R. Nuzum, M.D., and Leonard L. Rothschild, M.D., Santa Barbara, Calif.

The Vital Capacity in Hyperthyroidism with a Study of the Influence of Posture: A Preliminary Report. L. M. Rabinowitch, M.D., Montreal.

Studies on the Potassium Content of Human Serum. Lawson Wilkins, M.D., and Benjamin Kramer, M.D., Baltimore.

Some Unusual Disturbances of the Mechanism of the Heart Beat. Frank N. Wilson, M.D., and George R. Herrmann, M.D., Ann Arbor, Mich.

COPYRIGHT, 1933, BY THE AMERICAN MEDICAL ASSOCIATION

Med.
Wash

CONTENTS OF VOLUME 32

JULY, 1923. NUMBER 1

PAGE

METABOLIC STUDIES IN PERNICIOUS ANEMIA. R. R. GIBSON, PH.D., AND C. P. HOWARD, M.D., IOWA CITY 1

BLOOD PRESSURES IN FIFTEEN THOUSAND UNIVERSITY FRESHMEN. WALTER C ALVAREZ, M.D., ASSISTED BY ROSALIND WULZEN AND LUCILLE J. MAHONEY, SAN FRANCISCO 17

BLOOD CONCENTRATION CHANGES IN EXTENSIVE SUPERFICIAL BURNS AND THEIR SIGNIFICANCE FOR SYSTEMIC TREATMENT. FRANK P. UNDERHILL, PH.D., GEORGE L. CARRINGTON, M.D., ROBERT KAPSINOW, M.D., AND GEORGE T. PACK, M.D., WITH THE COOPERATION OF EPHRAIM SHORR, M.D., HENRY B. ROLLINS, M.D., FLORENCE I. PETERMAN, B.S., AND ALICE DIMICK, M.S., NEW HAVEN, CONN 31

OBSERVATIONS ON ONE HUNDRED AND NINETY-TWO CONSECUTIVE DAYS OF THE BASAL METABOLISM, FOOD INTAKE, PULSE RATE, AND BODY WEIGHT IN A PATIENT WITH EXOPHTHALMIC GOITER. CYRUS C. STURGIS, M.D., BOSTON 50

THE EFFECT OF ALKALIS ON GASTRIC SECRETION AND MOTILITY AS MEASURED BY FRACTIONAL GASTRIC ANALYSIS. BRUCE C. LOCKWOOD, M.D., AND HAZEN G. CHAMBERLIN, M.D., DETROIT 74

ACUTE LYMPHADENOSIS COMPARED WITH ACUTE LYMPHATIC LEUKEMIA. HAL DOWNEY, PH.D., AND C. A. MCKINLAY, M.D., MINNEAPOLIS 82

THREE FATAL ADULT CASES OF MALABSORPTION OF FAT WITH EMACIATION AND ANEMIA, AND IN TWO ACIDOSIS AND TETANY. HERMANN L. BLUMGART, M.D., BOSTON 113

CHYLOUS AND PSEUDOCHYLOUS EFFUSIONS: A REPORT OF SEVEN CASES. M. A. BLANKENHORN, M.D., CLEVELAND 129

THE CAUSES OF TURBIDITY IN MILKY ASCITIC FLUIDS. M. A. BLANKENHORN, M.D., CLEVELAND 140

AUGUST, 1923. NUMBER 2

WATER INTOXICATION. LEONARD G. ROWNTREE, M.D., ROCHESTER, MINN. 157

THE BENZOATE TEST FOR RENAL FUNCTION. II. F. B. KINGSBURY, PH.D., MINNEAPOLIS 175

A NEW METHOD FOR ACCURATELY DETERMINING THE CLOTTING TIME OF THE BLOOD. MORITZ F. PETERSEN, M.D., AND C. A. MILLS, M.D., CINCINNATI 188

THE INDUCTION OF PREMATURE CONTRACTIONS AND AURICULAR FIBRILLATION BY FORCED BREATHING ASSOCIATED WITH A CHANGE IN THE LOCATION OF THE PACEMAKER. FRED M. SMITH, M.D., AND WILLSON B. MOODY, M.D., CHICAGO 192

THE RELATIONSHIP OF EXCESS OF URIC ACID IN THE BLOOD TO ECZEMA AND ALLIED DERMATOSES BASED ON AN ANALYSIS OF OVER TWO HUNDRED CASES. JAY F. SCHAMBERG, M.D., AND H. BROWN, B.SC., PHILADELPHIA 203

A CLINICAL METHOD FOR THE ESTIMATION OF PROTEIN IN URINE AND OTHER BODY FLUIDS. MARIAN C. SHEVKY AND D. D. STAFFORD, M. A., SAN FRANCISCO 222

AUGUST, 1923—Continued

PAGE

STUDIES OF DIABETES MELLITUS. II. RESULTS OF TREATMENT BY DIET ADJUSTMENT WITH REFERENCE TO MAINTENANCE REQUIREMENT AND THE KETOGENIC-ANTIKETOGENIC BALANCE. WILLIAM S. MCCANN, M.D.; R. R. HANNON, M.D.; WILLIAM A. PERLZWEIG, PH.D., AND EDNA H. TOMPKINS, A.B., BALTIMORE 226

SOME INTERESTING CASES OF CALCAREOUS DEGENERATION FOUND IN THE THORAX. J. S. PRITCHARD, M.D., BATTLE CREEK, MICH 259

OBSERVATIONS ON SALT IN VASCULAR HYPERTENSION. JAMES P. O'HARE, M.D., AND WILLIAM G. WALKER, M.D., BOSTON 283

SPECIFIC TESTS IN THE DIAGNOSIS OF ALLERGY. W. W. DUKE, M.D., KANSAS CITY, MO 298

SEPTEMBER, 1923. NUMBER 3

THE MECHANISM OF PRODUCTION OF BREATH SOUNDS. P. MARTINI, M.D., MUNICH, GERMANY 313

SENSITIZATION TESTS WITH DIGESTIVE PRODUCTS OF PROTEIN. I. CHANDLER WALKER, M.D.; ARTHUR S. WETMORE, AND JUNE ADKINSON, A.M., BOSTON 323

THE VITAL CAPACITY OF THE CHINESE: AN OCCUPATIONAL STUDY. JOHN H. FOSTER, M.D., AND P. L. HSIEH, M.D., CHANGSHA, CHINA 335

BLOOD SUGAR REACTION FOLLOWING INTRAVENOUS INJECTION OF GLUCOSE. L. G. RIGLER, M.D., AND H. L. ULRICH, M.D., MINNEAPOLIS 343

EXPERIMENTS WITH HODGKIN'S DISEASE: AN ATTEMPT TO PRODUCE IT IN ANTHROPOIDS AND OTHER MONKEYS. W. F. CUNNINGHAM, M.D., AND KENNETH MCALPIN, M.D., NEW YORK 353

THE SIZE OF THE HEART IN PNEUMONIA: A TELEROENTGENOGRAPHIC STUDY, WITH OBSERVATIONS ON THE EFFECT OF DIGITALIS THERAPY. ROBERT L. LEVY, M.D., NEW YORK 359

DEFINITION OF HEMOLYTIC STREPTOCOCCUS PARASITISM IN THE UPPER AIR PASSAGES OF HEALTHY PEOPLE. ARTHUR L. BLOOMFIELD, M.D., AND AUGUSTUS R. FELTY, M.D., BALTIMORE 386

STUDIES ON LIVER FUNCTION: ROSE BENGAL ELIMINATION FROM THE BLOOD AS INFLUENCED BY LIVER INJURY. G. D. DELPRAT, JR., M.D., SAN FRANCISCO 401

THE BASAL METABOLISM DURING PREGNANCY AND THE PUERPERIUM. HOWARD F. ROOT, M.D., AND HESTER K. ROOT, BOSTON 411

TOXIC NEPHRITIS IN PYLORIC AND DUODENAL OBSTRUCTION: RENAL INSUFFICIENY COMPLICATING GASTRIC TETANY. GEORGE E. BROWN, M.D.; GEORGE B. EUSTERMAN, M.D.; HOWARD R. HARTMAN, M.D., AND LEONARD G. ROWNTREE, M.D., ROCHESTER, MINN 425

A CLINICAL REPORT ON ACUTE CASES OF MERCURIC CHLORID POISONING. L. C. GATEWOOD, M.D., AND ARTHUR F. BYFIELD, M.D., CHICAGO 456

STUDIES IN FAMILIAL NEUROSYPHILIS. III. CONJUGAL NEUROSYPHILIS (SECOND COMMUNICATION). JOSEPH EARLE MOORE, M.D., AND JAROLD E. KEMP, M.D., BALTIMORE 464

OCTOBER, 1923. NUMBER 4

BACTERIOLOGIC OBSERVATIONS ON ACUTE TONSILLITIS WITH REFERENCE TO EPIDEMIOLOGY AND SUSCEPTIBILITY. ARTHUR L. BLOOMFIELD, M.D., AND AUGUSTUS R. FELTY, M.D., BALTIMORE 483

ELECTROCARDIOGRAPHIC CHANGES FOLLOWING OCCLUSION OF THE LEFT CORONARY ARTERY. FRED M. SMITH, M.D., CHICAGO 497

OCTOBER, 1923—Continued

PAGE

STUDIES ON THE RABBIT'S HEART. I. EFFECT OF STROPHANTHIN ON THE SIZE OF THE NORMAL AND OF THE ABNORMAL HEART. G. F. STRONG, M.D., VANCOUVER, B.C., AND BURGESS GORDON, M.D., SPOKANE, WASH. 510

STUDIES ON THE RABBIT'S HEART. II. EFFECT OF VIGOROUS EXERCISE ON THE SIZE OF THE NORMAL AND THE ABNORMAL HEART. BURGESS GORDON, M.D., SPOKANE, WASH., AND G. F. STRONG, M.D., VANCOUVER, B.C. 517

GIARDIA INTESTINALIS INFECTION. EDWARD HOLLANDER, M.D., NEW YORK 522

GONORRHEAL MYELITIS. FRANK M. PHIFER, M.D., AND N. K. FORSTER, M.D. CHICAGO 530

MALIGNANT LYMPHOMA (HODGKIN'S DISEASE). A RADIOGRAPHIC STUDY. LESTER R. WHITAKER, M.D., CAMBRIDGE, MASS..... 538

CLINICAL AND ROENTGENOLOGIC STUDY OF ONE HUNDRED AND FIVE CASES OF SYPHILIS WITH REFERENCE TO THE CARDIOVASCULAR SYSTEM. EDWARD STEINFIELD, M.D.; GEORGE E. PFAHLER, M.D., AND JOSEPH V. KLAUDER, M.D., PHILADELPHIA..... 556

THE INFLUENZA EPIDEMIC AT CAMP DEVENS IN 1918: A STUDY OF THE PATHOLOGY OF THE FATAL CASES. S. BURT WOLBACH, M.D., AND CHANNING FROTHINGHAM, M.D., BOSTON..... 571

OBSERVATIONS ON CHANGES IN THE SIZE AND SHAPE OF HEARTS DURING THE PROGRESS OF COMPENSATION. J. C. FRIEDMAN, M.D., AND SIDNEY STRAUSS, M.D., CHICAGO..... 601

OBSERVATIONS ON THE INFLUENCE OF PITUITARY EXTRACT ON THE METABOLISM IN DIABETES INSIPIDUS. JAMES F. WEIR, M. D., ROCHESTER, MINNESOTA 617

GASTROSCOPY IN THIRTY CASES OF GASTRIC NEOPLASM. R. SCHINDLER, MUNICH, GERMANY 635

NOVEMBER, 1923. NUMBER 5

GENERAL RELATION BETWEEN SUSCEPTIBILITY AND PHYSIOLOGIC CONDITION. C. M. CHILD, M.D., CHICAGO..... 647

GASTRIC ULCER AND ACHLORHYDRIA. J. R. BELL, M.D., LONDON, ENG..... 663

CLINICAL OBSERVATIONS ON THE DYNAMICS OF VENTRICULAR SYSTOLE. I. AURICULAR FIBRILLATION. L. N. KATZ, M.D., AND H. S. FEIL, M.D., CLEVELAND 672

LAMBLIA (GIARDIA) INFECTION ASSOCIATED WITH CHOLECYSTITIS. REPORT OF A CASE TREATED WITH NEO-ARSPHENAMIN. J. L. KANTOR, M.D., NEW YORK 693

A STUDY OF THE BASAL AND NITROGENOUS METABOLISM IN A CASE OF ACUTE LEUKEMIA DURING ROENTGEN-RAY TREATMENT. W. G. LENNOX, M.D., AND J. H. MEANS, M.D., BOSTON..... 705

MELANURIA WITHOUT MELANOSARCOMA: REPORT OF A CASE. J. P. PETERS, M.D., NEW HAVEN, CONN..... 709

THE VALUE OF THE ELECTROCARDIOGRAPH IN PROGNOSIS. W. A. BLOEDORN, M.D., AND L. J. ROBERTS, M.D., WASHINGTON, D.C..... 718

EXPERIMENTAL INFECTIOUS STREPTOCOCCUS ENDOCARDITIS AND ITS ARSENICAL THERAPY (SODIUM CACODYLATE). J. A. BARGEN, M.D., CHICAGO 727

THE COMPLICATIONS OF STAPHYLOCOCCUS FOCAL INFECTIONS. LAIRD M. MORRIS, M.D., SAN FRANCISCO..... 746

A CONTRIBUTION TO THE BIOCHEMISTRY AND TREATMENT OF CHRONIC NEPHROSIS (EPSTEIN). I. M. RABINOWITCH, M.D., AND M. C. C. CHILDS, M.D., MONTREAL, CANADA..... 758

NOVEMBER, 1923—Continued

PAGE

A Study of the Blood Oxygen in Diabetes Mellitus. S. B. Grant, M.D., Boston 764
Gastric Secretion in Response to Duodenal Feeding. A. L. Garbat, M.D., New York..... 771
Digitalis Elimination. Harry Gold, M.D., New York..... 779
Observations on the Effects of Insulin in the Treatment of Diabetes Mellitus. I. M. Rabinowitch, M.D., Montreal, Canada 796

DECEMBER, 1923. NUMBER 6

The Importance of Our Knowledge of Thyroid Physiology in the Control of Thyroid Diseases. David Marine, M.D., New York.. 811
Elective Localization in the Eye of Bacteria from Infected Teeth. Russell L. Haden, M.D., Kansas City, Mo..... 828
Renal Injury Produced in Rabbits by Diets Containing Meat. L. H. Newburgh, M.D., and Sarah Clarkson, M.S., Ann Arbor, Mich.. 850
Periarteritis Acuta Nodosa. W. Ophüls, San Francisco..... 870
The Bacteriophage in the Treatment of Infections. Earl B. McKinley, M.D., Dallas, Texas..... 899
Subacute Bacterial Endocarditis Due to a Hemolytic Hemophilic Bacillus: Report of a Case. C. Philip Miller, M.D., and Arnold Branch, M.D., New York..... 911
The Urea Concentration Factor in the Estimation of Renal Efficiency. I. M. Rabinowitch, M.D., Montreal, Canada..... 927
Treatment by Splenectomy of Essential Thrombocytopenia (Purpura Hemorrhagica). N. E. Brill, M.D., and N. Rosenthal, M.D., New York 939
Blood Counts in Hodgkin's Disease: Report of a Case. Kenneth R. McAlpin, M.D., New York..... 954
The Etiologic Relation of Achylia Gastrica to Combined Sclerosis of the Spinal Cord: The Relief of Symptoms Following Adequate Hydrochloric Acid Therapy. Douglas Vanderhoof, M.D., Richmond, Va..... 958
Book Reviews: 972

Archives of Internal Medicine

VOL. 32 JULY, 1923 No. 1

METABOLIC STUDIES IN PERNICIOUS ANEMIA*

R. B. GIBSON, PH.D. AND C. P. HOWARD, M.D.

IOWA CITY

It should require considerable courage to add to the voluminous literature on the pathogenesis and chemistry of the so-called idiopathic pernicious anemia of Addison and Biermer. Our excuse is a threefold one:—first, to investigate with the aid of modern microchemical methods the metabolism of the blood lipoids as of probable diagnostic if not of etiological significance; second, to determine the nitrogen metabolism both in regard to its diagnostic as well as its prognostic value; and, third, to test the efficiency of Whipple's high iron diet when given to patients suffering from idiopathic anemia.

We have had the opportunity to study eleven cases of pernicious anemia, several of which have been available for considerable periods of time or during subsequent admissions. As controls, and in order to obtain comparative data on the anemias, four additional cases have been employed, a case of aplastic anemia with von Recklinghausen's disease, a pregnancy anemia, a hemolytic icterus case, and a splenic anemia.

1. GENERAL PROCEDURE

Each patient, after the usual clinical and laboratory investigation had established definitely the diagnosis, was transferred from the general medical ward to the special metabolic unit. There were available a special dietitian and two graduate nurses experienced in metabolic work. In this way a reasonable assurance can be given that the food intake and urine and fecal collections were carefully controlled.

Two diets have been employed in all except our earliest metabolic runs. These included fruits, green vegetables, lima beans, sweet potatoes, egg yolk and liver (daily), the constituents being selected to provide a ration rich in iron, and relatively low in fat. Diet 1 contained 10.64 gm. nitrogen and 45.6 mg. iron (by Wolter's modification of Neumann's method [1]) and yielded about 1900 calories. Diet 2 contained 12.04 gm. nitrogen, 26.9 mg. iron, and was equivalent to about

* From the Medical Clinic and the Research Laboratory of the Medical Clinic of the University Hospital, the State University of Iowa.

1. Wolter, O.: Ueber das Harneisen I. Die Bestimmung des Eisens in Harn, Biochem. Ztschr. **24**:108-124, 1910.

1,500 calories. This diet was planned for patients who could not consume completely the previous diet, or it was used increased by half at other times. Correction was made for extraneous iron in charcoal given to differentiate stools and in a yeast vitamin preparation used. Food not consumed was analyzed, and allowance made accordingly. While the iron values we have obtained for these diets are higher than the calculated values from the commonly available food tables, our figures were checked on diets prepared at different times and by several analysts; iron determinations on the urine and stools were made by the same method. An adequate vitamin supply and sufficient cholesterol, which is easily absorbed (Knudsen [2]) are provided in such a ration; cholesterol may have especial significance because of the low blood content of this substance in pernicious anemia along with its known antihemolytic action. The diets, in a way, are in accord with Thompson's recommendations [3] with a consideration of the work of Whipple and his associates on blood regeneration.

Blood samples for the study of the blood and plasma lipins were taken at the beginning and conclusion of the metabolic periods, and at such other times as the blood counts or the clinical course of the cases made further observations of interest.

Further details as to procedure will be given in the appropriate sections of this paper.

2. PLASMA AND BLOOD LIPINS WITH ESPECIAL REFERENCE TO IODIN ABSORPTION VALUES IN PERNICIOUS ANEMIA

The investigations of Schaumann,[4] Tallquist [5] and Faust [6] on the lipoid hemolytic substances of *Bothriocephalus latus* have had a profound influence on our views as to the origin of pernicious anemia. These investigators apparently proved conclusively that the active hemolytic substance is oleic acid (present in the worm as the cholesterol ester which made up 10 per cent. of the solids of the proglottides of

2. Knudson, A.: Relationship Between Cholesterol and Cholesterol Esters in the Blood During Their Absorption, J. Biol. Chem. **45**:255-262, 1921.

3. Carter, H. S.; Howe, P. E., and Mason, H. H.: Diet in Blood Diseases, Nutrition and Clinical Dietetics, Philadelphia, Lea & Febiger, Ed. 2, 1921, p. 536.

4. Schauman, O., and Tallquist, T. W.: Ueber die blutkoerperchenaufloesenden Eigenschaften des breiten Bandwurms, Deutsch. med. Wchnschr. **24**: 312-313, 1898.

5. Tallquist, T. W.: Zur Pathogenese der perniziösen Anaemie mit bes. Beruecksichtung der Bothriocephalusanaemie, Ztschr. f. klin. Med. **61**:427-532, 1907.

6. Faust, E. S., and Tallquist, T. W.: Ueber die Ursachen der Bothriocephalusanaemie, Arch. f. exper. Path. u. Pharmacol. **57**:367-385, 1907.

Faust, E. S.: Ueber chronische Oelsaurevergiftung, Arch. f. exper. Path. u. Pharmacol.: Suppl. Vol. 1908, pp. 171-175.

the parasites). The "lipoid substance" was strongly hemolytic in vitro. When injected into dogs and rabbits, it gave rather disappointing results, producing only a mild and transitory anemia of the secondary type; in fact, the anemia was so slight as to be attributable by impartial critics of the protocols to inanition and anorexia following the administration of any toxic substance. Further, it was discovered by Schmincke and Flury [7] that the dog's red cells acquired an immunity in vitro as well as in vivo to the hemolytic action of oleic acid. It is true that two years later Adler [8] reported the production in rabbits of blood crises resembling those of pernicious anemia by feeding nontoxic amounts of olive oil and cottonseed oil, both of which are, needless to say, rich in unsaturated fatty acids. A careful study of Adler's protocols, however, leaves one as nonenthusiastic, if not as entirely unconvinced, as did those of Faust and Tallquist. Joannovics and Pick [9] also attempted to explain hemolytic anemia by oleate hemolysis. They showed that as the result of subacute toluylendiamin poisoning in the dog, the ether soluble hemolytic substance (chiefly oleic acid) is increased in the liver to at least forty or fifty times the normal. They also found [10] in acute yellow atrophy and in phosphorus poisoning in man and animals that hemolysins of great activity could be obtained from the liver and that fatty acids could be found in large quantities in the blood. They explained the hemolytic effects of liver extracts in these conditions as due to the unsaturated fatty acid content.

Beumer and Bürger,[11] from their studies of the blood in pernicious anemia, chlorosis, leukemia and icterus, considered that the quantitative relations of the lipoids in the serum and corpuscles were of significance. They do not consider it definitely proven that the gastro-intestinal mucosa contains lipoids capable of producing anemia.

---

7. Schmincke, A., und Flury, F.: Ueber das Verhalten der Erythrocyten bei chronischen Oelsauerevergiftung, Arch. f. exper. Path. u. Pharmakol. **64**: 126-140, 1911.

8. Adler, H. J.: The Experimental Production of Pernicious Anemia in Rabbits, J. M. Research **23**:199-226, 1913.

9. Joannovics, G., and Pick, E. P.: Beitrag zur Kenntniss der Toluylendiaminvergiftung, Ztschr. f. exper. Path. u. Therap. **7**:185-214, 1909.

10. Joannovics, G., and Pick, E. P.: Ueber haemolytischwirkende freie Fettsaueren in den Leber bei akuten gelber Atrophie und Phosphorvergiftung, Berl. klin. Wchnschr. **47**:928-930, 1910.

11. Buerger, M., and Beumer, H.: Zur Lipoidschemie des Blutes I. Ueber die Verteilung von Cholesterin, Cholesterinestern und Lecithin in Serum, Berl. klin. Wchnschr. **50**:112-114, 1913.

Beumer, H., and Buerger, M.: II. Ueber die Zusammensetzung der Stromata menschlichen Erythrocyten mit besonderer Beruecksichtigung der Lipoide, Arch. f. exper. Path. u. Pharmak. **71**:311-328, 1913.

Beumer, H., and Buerger, M.: Beitraege zur Chemie des Blutes in Krankheiten mit besonderer Beruecksichtigung der Lipoide. III Mitteilung, Ztschr. f. exper. Path. u. Therap. **13**:343-361, 1913.

McPhedran[12] has demonstrated in a very convincing manner that the idea that toxic hemolysis in disease, in poisoning by phosphorus or toluylendiamin results from the liberation of specially hemolytic fatty acids from the fatty complexes of disintegrating cells is not well supported by evidence; none of the fatty acids, still less any of the fatty complexes from which these acids can be obtained in any of the organs examined, either in this work or in the work of others that has preceded it show on analysis any evidence for the existence of fatty acids more toxic than the common oleic acid which is constantly being set free by hydrolysis from common fat in health.

More recently Seyderhelm[13] has shown that it is not the lipoid fraction of the gastrophilus larvae (present in the stomach of the horse) nor of the bothriocephalus proglottis that is hemolytic in the body of the host; the alcoholic precipitate, however, is strongly hemolytic to the red cells of rabbits when introduced parenterally, though inactive in vitro. The composition of this blood poison is not given by Seyderhelm, but he has named it according to its origin "oestrin" and "bothriocephalin."

Finally, Beumer[14] has again tested out the hemolytic action of oleic acid by feeding young dogs (3 weeks old) in the belief that they might be more susceptible. As a matter of fact, the two dogs so tested revealed no anemia.

However, before the necessary time had elapsed to permit of the repetition and control of Faust and Tallquist's experiments, attempts were repeatedly made to assign the phenomena of idiopathic anemia to the presence of a powerful hemolysin circulating in the body presumably of a nonsaturated fatty acid nature. Consequently, the attention of the clinical investigators was directed to the study of the lipoids of the blood. Eppinger[15] in collaboration with King[16] and Medak[17] reported an increase in the total blood fats above the normal, while the free cholesterol was decreased to varying degrees. "The striking finding however, was the very high value for the iodin numbers. It is significant that the blood with the highest iodin number showed the lowest value in free cholesterin" (King). While the findings of Eppinger, King, and Medak as regards the low cholesterol figures have been sub-

12. McPhedran, W. F.: On the Hemolytic Properties of Fatty Acids and Their Relation to the Causation of Toxic Hemolysis and Pernicious Anemia, J. Exper. Med. **18**:527-542, 1913.

13. Seyderhelm, R.: Zur Pathogenese der pernizioesen Anaemia, Deutsch. Arch. f. klin. Med. **126**:95-147, 1918.

14. Beumer, H.: Zur pathogenetischen Bedeutung der Oelsauere bei Anaemien, Biochem. Ztschr. **95**:239-248, 1919.

15. Eppinger, H.: Zur Pathologie der Milzfunktion (I Mitteilung), Berl. klin. Wchnschr. **50**:1509-1512, 1572-1576, 1913.

16. King, J. H.: Studies in the Pathology of the Spleen, Arch. Int. Med. **14**: 145-167 (Aug.) 1914.

17. Medak, E.: Beitrag zur Chemie des Blutes bei anaemischen Krankheitbildern, Bioch. Ztschr. **59**:419-428, 1914.

stantiated by Feigl [18] and by Rosenthal and Holzer [19] in Germany, and by Csonka,[20] Bloor and MacPherson,[21] Denis [22] and Kipp [23] in America, their conclusions have not escaped the criticism of Feigl and of Rosenthal and Holzer as one might expect from McPhedran's observations previously quoted. The main cause for criticism is the high iodin number for the blood fat found by Eppinger et al. However, if one takes into account the definite statement that the iodin values are multiplied by ten with the probable purpose to establish a pro mille basis, their figures are not actually high as compared with those of other observers. Yet one must admit that Eppinger et al. considered them abnormally high and stated that their results "suggested that hemolysis was due to the unsaturated fatty acids." At the beginning of our work, we felt in accord with Bloor and MacPherson who wrote that

> While the results offer no certain evidence that abnormalities in the blood lipoids are responsible for anemia, the low values of the cholesterol, which is an antihemolytic substance, and the high fat fraction, which may indicate the presence of abnormal amounts of hemolytic lipoids in the blood, are possible causative factors, of which further investigation is desirable.

We have made iodin absorption, fatty acid and cholesterol determinations on the whole blood and plasma in our series of cases. For the iodin values, one of us (Gibson) has adapted the Hanus method for micro-analysis, using the filtrates from the Bloor blood fat extraction after the fat and cholesterol (Autenrieth and Funk) have been determined. We have thus been able to obtain figures for the nonsaturated fatty acid groups at more frequent intervals than if we had to employ large quantities of blood for the usual determination of the iodin number.

> Three cubic centimeters of whole blood or plasma are extracted with alcohol-ether mixture and the filtrates made up to 100 c.c. as in Bloor's method.[21] Duplicate extractions are made. Ten cubic centimeters from each extraction are used for nephelometric determination of the blood fat, and 10 c.c. more for the cholesterol. The 80 c.c. remaining are evaporated in a glass dish on the steam bath, and removed just as dryness is reached. The residues are washed three times with 10 c.c. of chloroform, each time pouring through small filters into 100 c.c.

18. Feigl, J.: Ueber das Vorkommen und die Verteilung von Fetten und Lipoiden in menschlichen Blute bei toxaemischen (haematinaemischen) Krankheitzustaenden, Bioch. Ztschr. **93**:257-288, 1919.

19. Rosenthal, F., und Holzer, P.: Beitraege zur Chemie des Blutes bei anaemischen Krankheitzustaenden, Biochem. Ztschr. **108**:220-234, 1920.

20. Csonka, F. A.: A Critique of Certain Data on the Content of Cholesterol and Fatty Substances in the Blood, etc., J. Biol. Chem. **24**:431-438, 1916.

21. Bloor, W. R., and MacPherson, D. J.: The Blood Lipoids in Anemia, J. Biol. Chem. **31**:79-95, 1917.

22. Denis, W.: Cholesterol in Human Blood Under Pathologic Conditions, J. Biol. Chem. **29**:93-110, 1917.

23. Kipp, H. A.: The Effect of Whole Blood Transfusion on the Cholesterol Content of Human Serum in Pernicious Anemia, J. Biol. Chem. **43**:413-420, 1920.

Ehrlenmeyer flasks. The flasks are then placed on the steam bath and evaporated just to dryness, so that when removed from the bath enough chloroform condenses within the flask to take up the fat residues. One c.c. of chloroform is added to each flask and to three control flasks, 2 c.c. exactly of Hanus' iodin solution is introduced into each one of the series, the contents thoroughly mixed by rotating, corked and placed in a dark locker for one hour. Fortieth normal sodium thiosulphate solution is used for the titration after adding 0.5 c.c. of 15 per cent. potassium iodid solution and 10 c.c. of water, with starch paste employed as an indicator toward the end of the titration in the usual way. The titration difference × 0.305 divided by the grams of fat in the alcohol-ether extract used equals the iodin number. The iodin absorbed per 100 c.c. of blood may be taken as an indication of the nonsaturated fatty acid groups present.

We did not find, as did King and also Bloor, abnormally high blood fats in our pernicious anemia cases (Table 1). In fact, very low blood and plasma fat contents accompanied the severe anemic condition in Cases 1, 4, 10 and 11, and these were increased with improvement in the blood picture. Very small fat figures have been found in pernicious anemia (two cases studied) by Denis [24] also. The low blood fats seem to be associated with higher iodin numbers in the pernicious anemia cases, though the amounts of the unsaturated fatty acid groups as evidenced by the total iodin absorbed were small. Case 7, with a red blood cell count of less than one million and a hemoglobin of 25 per cent., had a normal fat, iodin number of 64, and the iodin absorbed was 0.43 gm. per 100 c.c. of blood; very similar figures obtain for Case 6 with an anemia of mild degree only. The highest concentration of nonsaturated fatty acid groups (0.86 gm.) appears in the aplastic anemia case (Case 12) in the analysis of the whole blood sample for March 7.

Blood and plasma cholesterol figures were low in the pernicious anemia cases with pronounced anemia, and tended to increase to normal as the blood regenerated. High cholesterol figures were found for Case 6, a patient with marked cord changes, but with a mild degree of anemia only. Three out of the four pathologic control cases (Cases 12, 13 and 14) showed a normal or high cholesterol; it is of particular interest that the fourth control (Case 15), a case of splenic anemia, had low plasma and blood cholesterol figures.

We consider that our results are in accord with Feigl's as well as Rosenthal and Holzers' observations.

While our results indicate that an increase in the unsaturated fatty acids in the blood cannot be a factor for hemolysis in pernicious anemia, the problem has been attacked in a different way. Recently Ashby [25]

24. Denis, W.: The Influence of Splenectomy on Metabolism in Anemia, Arch. Int. Med. **20**:79-92 (July) 1917.

25. Ashby, W.: Study of Transfused Blood, J. Exper. Med. **34**:127-146; 147-166, 1921.

TABLE 1.—*Fat, Cholesterol and Iodin Absorption Vaults for Whole Blood and Plasma*

Case	Date	R. B. C.	Hbg.	R. B. C. Pl.	Plasma				Blood			
					Chol.	Fat	I_2 No.	I_2 %	Chol.	Fat	I_2 No.	I_2 %
1. McG.	2/24/20	1,910	40	.....	....	....	..	....	0.10	0.34	72	0.37
Pernicious	3/19/20	2,000	50	.....	....	....	..	....	....	0.58	87	0.50
anemia	10/12/20	930	25	.....	....	....	..	....	0.07	0.53	41	0.22
	10/16/20	660	18	.....	....	....	..	....	0.08	0.35	53	0.19
	12/10/20	2,900	70	.....	0.17	0.68	59	0.40				
2. M'd.	4/19/20	1,970	65	.....	....	....	..	....	0.15	0.50	73	0.36
Pernicious anemia												
3. Mn.	4/10/20	2,400	70	.....	....	....	..	....	0.18	0.51	88	0.45
Pernicious anemia												
4. Mat.	12/ 9/20	1,200	30	9:91	0.11	0.25	..	....	0.15	0.29	95	0.27
Pernicious	12/22/20	1,980	40	21:79	0.15	0.63	53	0.33	....	0.45	60	0.27
anemia	1/ 8/21	1,790	47	30:70	0.17	0.55	60	0.33	....	0.49	73	0.35
	1/24/21	2,640	78	33:67	0.21	0.50	51	0.26				
	2/ 1/21	3,170	65	.....	....	....	..	....	0.26	0.58	56	0.32
	3/ 7/21	3,120	80	30:70	0.19	0.50	88	0.44	0.22	0.60	73	0.44
5. Baugh.	1/18/21	3,080	74	30:70	0.19	0.67	30	0.20				
Pernicious anemia	2/ 7/21	2,910	70	.....	0.16	0.50	56	0.28	0.18	0.60	65	0.39
6. Bibg.	1/25/21	4,090	85	40:60	0.27	0.70	40	0.28				
Pernicious	2/ 1/21	4,520	92	.....	....	....	..	....	0.28	0.67	66	0.44
anemia;	3/ 7/21	4,290	100	46:54	0.25	0.81	65	0.53	0.29	0.70	68	0.47
splenectomy	5/10/21	4,800	100	45:55	0.29	0.65	80	0.52	0.32	0.65	94	0.54
	8/16/21	5,280	95	.....	0.31	0.68	74	0.50	0.27	0.70	88	0.62
7. W.	3/22/21	990	25	11:89	0.14	0.58	75	0.41	0.16	0.67	64	0.43
Pernicious anemia												
8. Dug.	10/22/21	2,620	54	32:68	0.21	0.67	95	0.65	0.18	0.60	107	0.64
Pernicious	10/30/21	3,260	68	.....	0.16	0.67	81	0.54	0.19	0.63	80	0.50
anemia	11/ 7/21	3,180	70	38:62	0.16	0.67	71	0.48	0.19	0.58	86	0.50
	11/29/21	4,050	80	42:58	0.21	0.89	71	0.41	0.25	0.60	87	0.52
9. Mill.	11/ 7/21	2,180	50	36:64	0.21	0.64	82	0.49	0.20	0.46	109	0.50
Pernicious	11/15/21	2,210	50	.....	0.19	0.52	86	0.40	0.20	0.46	85	0.44
anemia	11/22/21	2,790	65	39:61	0.16	0.51	70	0.41	0.23	0.65	81	0.46
	11/29/21	2,820	65	.....	0.16	0.57	89	0.51	0.17	0.62	82	0.51
10. Sch.	12/ 5/21	925	23	17:83	0.09	0.35	101	0.36	0.14	0.47	77	0.36
Pernicious	12/12/21	1,410	35	25:75	0.11	0.37	85	0.32	0.17	0.34	101	0.35
anemia	12/19/21	2,620	56	26:74	0.20	0.55	78	0.43	0.17	0.54	77	0.42
11. Han.	3/30/22	1,110	26	13:87	0.092	0.35	65	0.23	0.16	0.38	63	0.24
Pernicious	4/ 3/22	1,020	30	18:82	0.14	0.39	99	0.40	0.18	0.68	65	0.44
anemia;	4/ 7/22	2,200	44	21:79	0.16	0.41	89	0.30	0.15	0.35	108	0.38
syphilis												
12. Boy.	12/22/20	3,600	45	.....	0.30	0.50	60	0.33	....	0.62	63	0.41
Aplastic	2/ 7/21	3,590	40	.....	0.20	0.62	47	0.29	0.21	0.77	54	0.42
anemia	3/ 7/21	4,320	65	33:67	0.33	0.72	76	0.54	0.44	0.90	95	0.86
13. Cook.	3/ 1/21	1,690	40	16:84	0.21	0.57	80	0.47	0.27	0.58	82	0.48
Pregnancy;	3/ 9/21	1,320	45	19:81	0.19	0.39	94	0.36	0.22	0.44	84	0.37
anemia	3/18/21	2,550	43	21:79	0.20	0.52	70	0.36	0.24	0.58	71	0.43
14. Hel.	2/17/21	4,444	92	48:52	0.29	0.64	83	0.53	0.38	0.65	90	0.59
Hemolytic icterus; splenectomy												
15. Plom.	12/ 5/21	2,600	40	20:80	0.09	0.44	70	0.40	0.15	0.54	73	0.40
Splenic	12/10/21	.....	32	18:82	0.09	0.31	92	0.29	0.10	0.34	84	0.29
anemia	12/17/21	1,480	30									

studied the length of life of transfused corpuscles in pernicious anemia and concluded that there was no hemolytic toxin producing the anemia in this disease. Wearn, Warren and Ames [26] have confirmed Ashby's experimental observations, though conservatively questioning her conclusion. They have found also in a single observation that red blood corpuscles from a patient with pernicious anemia when transfused into another patient with pernicious anemia behaved as did the corpuscles from normal donors.

3. NITROGEN AND IRON BALANCES AND THE NITROGEN PARTITION

Metabolic studies on pernicious anemia were first directed to the nitrogen balance. Neither von Noorden [27] nor Halpern [28] was able to show that protein catabolism was increased characteristically in this condition, while Rosenquist [29] found periods in which increased nitrogen excretion and retention alternated. According to Mohr,[30] a nitrogen retention may obtain in some cases even on a low protein intake, and in others a loss of nitrogen may be observed when a high protein diet is given; the nitrogen exchange is not dependent on the diminution of the hemoglobin. The difficulty in obtaining nitrogen balances is evident in the later contributions on the anemias with or without splenic disease (Umber,[31] Minot,[32] McKelvey and Rosenbloom,[33] Goldschmidt and Pearce,[34] Goldschmidt, Pepper and Pearce,[35] Pepper and Austin [36])

---

26. Wearn, J. T.; Warren, S., and Ames, O.: The Length of Life of Transfused Erythrocytes in Patients with Primary and Secondary Anemia, Arch. Int. Med. **29**:527-538 (May) 1922.

27. Cited by Strauss, H.: Der Einfluss der Blutkrankheiten auf die Eiweisszersetzung der Purinkoerper und Salzstoffwechsel, v. Noordens Handb. d. Path. u. Stoffwechsels: Berlin, A. Hirschwald, **1**:891-895, 1906.

28. Halpern, M.: Zur Frage der Stickstoffvertheilung im Harn in pathologischen Zustaenden, Ztschr. f. klin. Med. **50**:355-376, 1903.

29. Rosenquist, E.: Ueber den Eiweisstoffwechsel bei der pernicioesen Anaemie, Ztschr. f. klin. Med. **49**:193-320, 1903.

30. Mohr, L.: Gesamtstoffwechsel bei Anaemien, Kachexien, u. s. w. Handb. d. Biochem. d. Menschen u. d. Thiere: Jena, G. Fischer, **4**:381-392, 1910.

31. Umber, F.: Zur Pathogenese der Bantischen Krankheit mit besonderen Beruecksichtung des Stoffumsatzes, u. s. w., Ztschr. f. klin. Med. **55**:289-314, 1904.

32. Minot, G. R.: Nitrogen Metabolism Before and After Splenectomy, etc., Bull. Johns Hopkins Hosp. **26**:338-342, 1914.

33. McKelvy, J. P., and Rosenbloom, J.: Metabolism Study of a Case of Hemolytic Jaundice, etc., Arch. Int. Med. **15**:227-238 (Feb.) 1915.

34. Goldschmidt, S., and Pearce, R. M.: Studies of Metabolism in the Dog Before and After Removal of the Spleen, J. Exper. Med. **22**:319-331, 1915.

35. Goldschmidt, S.; Pepper, O. H. P., and Pearce, R. M.: Metabolism Studies Before and After Splenectomy in Congenital Hemolytic Icterus, Arch. Int. Med. **16**:437-455 (Sept.) 1915.

36. Pepper, O. H. P., and Austin, J. H.: Metabolism Studies Before and After Splenectomy in a Case of Pernicious Anemia, Arch. Int. Med. **18**:131-135 (July) 1916.

though slight nitrogen retention may occur. Positive nitrogen balances are indicated in Denis'[24] series of anemia cases, both before and after splenectomy; the diet was high caloried but low in protein. Mosenthal[37] readily obtained a favorable nitrogen balance with improvement in the blood picture for three cases of pernicious anemia and one case of secondary anemia when given high protein and energy diets.

Von Noorden found a lower percentage of the total nitrogen excretion as urea nitrogen for some cases, though he cites higher figures from earlier workers. Minot's case before transfusion and splenectomy had a very low urea nitrogen elimination—on one day only 34.5 per cent. of a total nitrogen of 14.6 gm. Figures cited by von Noorden from the older literature for the ammonia nitrogen excretion are normal or relatively low; ammonia nitrogen averaged 0.42 gm. per day in Minot's case and still less in Denis' cases. Uric acid elimination is variable, Rosenquist reporting minimal and maximal purin nitrogen (endogenous) of from 0.173 to 0.409 gm. In the later literature, Pepper and Austin and also Denis give uric acid figures for pernicious anemia; the daily excretion may be rather high, but not abnormally so. Kahn and Barsky[38] consider the nitrogen fractions of the urine normal, except for an increased elimination of oxyproteic acid nitrogen; conjugated sulphates and neutral sulphur were increased.

As the result of splenectomy preceded by a transfusion, the slightly negative nitrogen balance in Minot's case was changed over to a slight retention; the urea nitrogen was increased from an average of 54.3 per cent. to 79.6 per cent. of the total nitrogen, but there was no change in the ammonia nitrogen excretion. Pepper and Austin obtained a more favorable nitrogen balance and a drop in the uric acid excretion as the result of transfusion and splenectomy; the daily iron elimination in the stool fell from 17 to 10 mg. The effects of splenectomy were not constant in Denis' observations, nor were the sulphur partition figures significant.

Gettler and Lindeman[39] found in thirty-two cases of pernicious anemia blood and nonprotein nitrogen, urea nitrogen, and creatinin values higher than normal; uric acid figures were quite high, and the amino-acid nitrogen was increased also. The blood sugar, too, was abnormally high.

---

37. Mosenthal, H. O.: The Effect of Forced Feeding on the Nitrogen Equilibrium and Blood in Pernicious Anemia, Bull. Johns Hopkins Hosp. **29**: 129-134, 1918.

38. Kahn, M., and Barsky, J.: Studies of the Chemistry of Pernicious Anemia, Arch. Int. Med. **23**:334-345 (March) 1919.

39. Gettler, A. O., and Lindeman, E.: Blood Chemistry of Pernicious Anemia, Arch. Int. Med. **26**:453-458 (Oct.) 1920.

Peters and Rubnitz [40] determined the total nitrogens of the whole blood and of the blood plasma of four cases of pernicious anemia; the determination of course includes the protein nitrogen. Inasmuch as the corpuscles are richer in total nitrogen content than the plasma, the total nitrogen of which remains within normal limits or tends to increase, they establish a "nitrogen index" or ratio of the whole blood nitrogen to the plasma nitrogen; this is diminished in proportion to the degree of anemia and may therefore be used as an indication of the state and progress of the anemic condition.

Our own work has been directed chiefly to the study of the nitrogen and iron balances when the "pernicious anemia diet" was given; figures on the nitrogen partition were also obtained. These data are summarized in Table 2. Figures are averages of four or five day periods. No medication was employed while the patients were in the metabolism unit, and the diet was given two or three days or longer previous to actually starting the balance runs. The commonly used analytical procedures were followed for the determinations of the nitrogen partition. Because of the undigested food residues frequently appearing in the pernicious anemia stools and due to the characteristically deficient gastric secretion, it was necessary to use the dried and thoroughly ground feces for analysis.

The total nitrogen elimination is not excessive. On a very moderate protein intake of from 61 to 75.5 gm. and with a relatively low calorie value, Cases 2, 3, 4 (Period 1), 6 (Period 2, after splenectomy), 7, 8 (Period 2) and 9 have given positive nitrogen balances. Cases 10 and 11, on a higher protein intake, have eliminated a greater amount of nitrogen, as might be expected, but have shown a favorable balance. Slight or moderate nitrogen losses obtained for Cases 1, 4 (Periods 2 and 3), 6 (Period 1) and 8 (Period 2), while a considerable nitrogen excretion and loss occurred for Case 5. Of the controls, Case 14 (hemolytic icterus) showed consistently a negative nitrogen balance, though the nitrogen excretion was markedly diminished in the post-splenectomy Period 3; the diets for Periods 1 and 3 were probably too low in calories, the patient being a large man and active at these times.

In the case of the iron balances, it might be expected that the results would be influenced by the deposition in or discharge of stored iron from the tissues. However, the iron balances quite consistently follow the gain, the stationary state or the fall in blood cell counts and hemoglobin percentages. Thus favorable iron balances were observed for Cases 1 (Period 2), 2, 4, 5, 6 (increased after splen-

40. Peters, A. W., and Rubnitz, A. S.: Observations on the Chemical Pathology of the Blood in Pernicious Anemia, Arch. Int. Med. **26**:561-569 (Oct.) 1920

TABLE 2.—*Nitrogen and Iron Balances and Nitrogen Partition*

Case		Period	Total N, Gm.	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Balances		Food				
				Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	N, Gm.	Fe, Mg.	Prot., Gm.	Fat, Gm.	Chhy., Gm.	Total, Cal.	Fe, Mg.
1. McG.	1	2/17-21/20	8.75	.....	....	.....	....	0.380	4.36	0.326	3.74	0.022	0.26	—0.21	— 6.3	61	34	284	1,684	27.7
	2	3/ 4- 8/20	8.80	.....	....	.....	....	0.393	4.46	0.292	3.34	0.049	0.54	—0.59	+ 4.3*	61	34	284	1,684	27.7
	3	10/13-15/20	12.16	7.90	65.0	0.482	3.97	0.307	2.53	0.468	3.85	0.189	1.55	.....	.....	†				
2. M'd.	1	4/16-19/20	10.57	7.54	71.3	0.620	5.87	0.289	2.73	0.427	4.13	0.000	0.00	+0.47	+10.7*	74	64	276	1,977	42.4
	2	5/11-14/20	9.80	7.99	81.5	0.701	7.15	0.244	2.49	0.411	4.20	0.000	0.00	+1.59	+21.3	75	50	324	2,052	35.2
3. Mn.	1	4/ 7-10/20	8.09	6.02	81.7	0.530	6.55	0.283	3.50	0.338	4.18	0.000	0.00	+1.57	+ 0.1	62	45	231	1,570	24.0
4. Mat.	1	12/19-22/20	9.38	6.64	70.8	0.388	4.13	0.596	6.35	0.402	4.28	0.000	0.00	+0.06	+22.6	67.5	39.6	305	1,896	45.6
	2	2/ 7-12/21	9.75	7.45	76.6	0.427	4.38	0.228	2.34	0.376	3.86	0.050	0.51	—1.13	+ 1.5	67.5	39.6	305	1,896	45.6
	3	4/ 9-14/21	9.50	6.97	71.5	0.332	3.49	0.233	2.45	0.396	4.17	0.021	0.22	—1.45	+10.5	67.5	39.6	305	1,896	45.6
5. Baugh.	1	1/19-24/21	12.49	8.52	68.3	0.528	4.23	0.374	3.00	0.503	4.03	0.057	0.45	—3.47	+ 7.7	67.5	39.6	305	1,896	45.6
6. Bibg.	1	1/25-29/21	8.78	6.21	70.7	0.532	6.06	0.229	2.61	0.574	6.54	0.054	0.61	—0.81	+ 2.3	67.5	39.6	305	1,896	45.6
	2	5/12-17/21¶	6.45	3.85	61.1	0.270	4.19	0.148	2.30	0.585	9.00	0.000	0.00	+2.24	+12.4	67.5	39.6	305	1,896	45.6
7. W.	1	5/ 3- 8/21	5.44	2.81	51.7	0.353	6.49	0.265	4.86	0.120	2.21	0.043	0.79	+3.37	+23.3	67.5	39.6	305	1 896	45.6
8. Dug.	1	10/26-29/21	8.34	7.00	83.90	0.586	7.04	0.211	2.60	0.269	3.23	0.000	0.00	+0.15	—32.9	67.5	39.6	305	1,896	45.6
	2	11/ 2- 6/21	8.85	6.51	73.62	0.687	7.77	0.181	2.04	0.271	3.07	0.000	0.00	—0.21	— 8.5	68	68.6	305	2,167	49.7
9. Mill.	1	11/ 9-11/21	7.05	5.64	80.00	0.670	11.97	0.154	2.24	0.170	3.04	0.000	0.00	.....	.....	67.6	39.6	304	1,896	45.6
	2	11/15-19/21	9.78	.....	....	.....	....	.....	....	0.185	....	.....	....	+0.36	+16.2	75.4	35	205.7	1,521	35.8
	3	11/23-27/21	9.98	.....	....	.....	....	.....	....	0.178	....	.....	....	+0.47	+ 1.1	75.4	70	205.7	1,846	35 8
10. Sch.	1	12/ 7-12/21	7.17	5.03	70.18	0.366	5.10	0.275	3.83	0.289	4.03	0.000	0.00	.....	.....	75.4	70	205.7	1 846	35.8
	2	12/17-20/21	9.04	6.95	76.80	0.479	5.31	0.228	2 53	0.233	2.58	0.000	0.00	.....	.....	75.4	70	205.7	1,846	35.8
	3	12/21-24/21	9.25	7.28	78.81	0.525	5.68	0.231	2.50	0.239	2.58	0.000	0.00	.....	.....	75.4	70	205.7	1,846	35.8
	4	1/12-16/22	13.71	.....	....	.....	....	.....	....	0.228	....	.....	....	+2.30	+ 0.7	113	53	307	2,157	50.0
	5	1/16-19/22	14.00	.....	....	.....	....	.....	....	0.276	....	.....	....	+1.28	— 5.3	113	88	307	2,472	46 0
11. Han.	1	3/31-4/3/22	14.21	.....	....	.....	....	0.340	....	0.366	....	0.027	....	+2.10	+13.4	113	53	307	2,157	43.7
	2	4/ 4- 7/22	14.38	11.98	83.31	0.479	3.33	0.390	2.71	0.375	2.61	0.000	0.00	+2.13	+16.6	113	88	307	2,472	42.3
12. Boy.	1	12/19-22/20	6.81	4.37	63.7	0.637	9.35	0.373	5 47	0.314	4.61	0.022	0.32	+1.79	+21.8	67.5	39.6	305	1,896	45.6
13. Cook.	1	3/ 2- 5/21	6.96	4.84	69.5	0.360	5.17	0.323	4.78	0.324	4.65	0.068	0.98	—0.45	+ 1.6	67.5	39.6	305	1,896	45.6‡
	2	3/ 9-14/21	9.29	6.93	74.6	0.245	2.64	0.390	4.20	0.350	3.88	0.091	0.87	+1.51	+ 3.8	67.5	39.6	305	1,896	45.6§
14. Hel.	1	2/ 3- 7/20	14.14	10.99	77.7	0.699	4.94	0.194	1.37	0.677	4.79	0.000	0.00	—1.06	+13.7	79	111	208	2,152	29.7
	2	3/ 1- 5/20¶	15.18	.....	....	.....	....	0.317	2.09	0.543	3.57	0.000	0.00	—2.81	+ 5.2	79	111	208	2,152	29.7
	3	2/17-20/21	11.47	8.28	72.2	0.516	4.50	0.212	1.85	0.585	5.10	0.038	0.33	—1.67	+25.0	67.5	39.6	305	1,896	45.6
15. Plom.	1	11/30-12/4/21	8.83	7.05	80.6	1.012	11.35	0.212	2.40	0.394	4.46	0.000	0.00	+0.55	— 1.7	67.5	39.6	305	1 896	45.6
	2	12/ 8-13/21#	8.52	.....	....	.....	....	0.250	....	0.405	....	.....	....	.....	.....	67.5	39.6	305	1,896	45.6

* Iron balances in these starred figures are from food and stool determinations; the urines were not done or were lost in these cases. It is probable the urines did not contain over a milligram or two per diem

† Very little eaten. ‡ About one fourth refused. § A little refused. ¶ Splenectomy. # After gout attack.

ectomy), 7, 9 and 11, with coincident betterment of the blood picture. Approximate iron equilibrium was found for Case 3 and for case 10 when little change in the blood findings obtained. Case 8 exceptionally presented a considerable loss of iron during the first period and a much less figure for the second period; an increase in the blood count with little change in the hemoglobin percentage was recorded at this time. The nonpernicious anemia cases all showed favorable iron balances except the splenic anemia case, for which a slight iron loss of 1.7 mg. per day was noted. That positive iron balances may accompany a daily loss of nitrogen to the body is shown in the data for Cases 1 (Period 2), 4 (Periods 2 and 3), 5 and 6 (Period 1), and for the nonpernicious Cases 13 (Period 1) and 14.

In four of our studied cases of pernicious anemia (Cases 8, 9, 10 and 11) we have tried the effect of the addition of a moderate amount of fat to the diet. In view of a possible marked stimulation of hemolysis—though not indicated by our blood studies—we have employed butter as the source of the fat since this has a moderate iodin absorption value only. The less favorable figures obtained for Cases 9 and 10 suggest that further investigation of fat ingestion in pernicious anemia should be carried out.

As regards the nitrogen partition, the pernicious anemia cases tend to show low urea nitrogen figures. Moderate or low ammonia nitrogen figures may be found—Cases 1, 4, 5, 6 after splenectomy, 7, 10 and 11. Rather high uric acid nitrogen figures obtain, even when the patients were on a nonpurin diet (Cases 1, 2 and 3); exceptions are Case 6 after splenectomy, Case 8 (Period 2), and Case 9. Of the other anemias, the aplastic Case 12 presented a nitrogen partition similar to that of pernicious anemia, except for the ammonia figures, while the pregnancy anemia Case 13 is quite suggestive of the pernicious anemia findings. The hemolytic icterus Case 14 gave a low urea nitrogen percentage of the total nitrogen, but the other constituents are normal for Period 1; an ultimate effect of splenectomy is not reflected in the nitrogen partition figures for Period 3. The splenic anemia Case 15 picture was characterized by a high ammonia excretion only; following an attack of gout, the uric acid elimination was somewhat increased.

Our findings may be summarized briefly for this section. Favorable nitrogen, and especially iron, balances have been established in pernicious anemia and in some other types of clinical anemias (excepting iron in our case of splenic anemia) when given diets rich in food iron and with comparatively low calorie and protein values. Slightly negative nitrogen balances and coincident iron retention may obtain. Low urea nitrogen excretion and low or moderate ammonia nitrogens along

with rather high uric acid nitrogen figures are characteristic but not constant findings; these results are in general accord with most of the figures available in the literature.

4. IMMEDIATE EFFECTS OF BLOOD TRANSFUSION ON METABOLISM

Cases 1 and 2 were transfused with from 450 to 500 c.c. of blood (citrated) of the same grouping while under observation in the metabolism unit. The immediate effect of the transfusion was a pronounced stimulation of the nitrogen catabolism. The increased excretion of the total, urea, uric acid and creatinin nitrogens continued over the succeeding two days. The figures are given in Table 3.

TABLE 3.—*Effects of Transfusion of Blood of Similar Grouping*

Case	Period	Total N, Gm.	Urea N, Gm.	Am. monia N, Gm.	Uric Acid N, Gm.	Creatinin N, Gm.	Creatin N, Gm.	Food			
								Protein, Gm.	Fat, Gm.	Chhy., Gm.	Total, Cal.
1. McG. (1)	2/22/20	8.06	.....	.....	0.389	0.279	0.097	62	32	285	1,679
	2/23/20	8.86	.....	.....	0.391	0.274	0.045	68	35	253	1,575
	2/24/20*	9.52	.....	.....	0.383	0.353	0.059	52	23	245	1,401
	2/25/20	10.92	.....	.....	0.459	0.334	0.058	63	35	307	1,792
	2/26/20	12.42	.....	.....	0.370	0.305	0.102	62	36	302	1,781
	2/27/20	10.08	.....	.....	0.408	0.285	0.022	62	30	231	1,524
2. M'd.	4/24-27/20	8.27	6.50	0.440	0.276	0.437	0.000	64	44	294	1,877
	4/28/20*	5.25	3.61	0.284	0.185	0.434	0.000	†			
	4/29/20	13.72	10.12	0.435	0.324	0.570	0.000	39	40	161	1,109
	4/30/20	13.89	11.53	0.435	0.404	0.471	0.000	64	51	224	1,650

* Transfused. † Breakfast only.

5. FAT UTILIZATION AND STOOL FATS IN ANEMIA CASES

We present some data on the food and stools fat, including the iodin absorption numbers, and the utilization of the ingested fat in this series of cases. The results are given in Table 4.

Sherman [41] gives the average normal fat utilization or "coefficient of digestibility" as 95 per cent. Of course, this factor varies with the amount of fat in the diet, since diets free from fat yield stools which contain appreciable amounts of ether soluble substances. In view of this fact, a utilization of fat of from 72 to 89 per cent. by our pernicious anemia cases is very satisfactory.

There is no definable relation between the character or degree of the anemia and the partition or the iodin values of the stool fats. Though considerable variation was found, the iodin numbers were all comparatively low. While it is probable that the iodin values of the stool fats have been lessened because of the dessication of the stools for the nitrogen and iron determinations, the food fats were subjected to

41. Sherman, H. C.: Comparative Digestibility of Fats, Foods Products, New York, McMillan & Co., 1917, p. 393.

the same procedure; again, iodin numbers obtained on the lipin extracts of a fresh stool (Case 1, Period 3) were quite similar to the other values obtained. Our data afford no evidence of the intestinal formation of fatty acids of high iodin values in pernicious anemia.

DISCUSSION

Dietetic deficiency in the sense of avitaminosis has not been considered an etiologic factor in pernicious anemia, though Fayrer [42] (in 1888) suggested that pernicious anemia in Europe resembled beriberi

TABLE 4.—*Fat Utilization and Stool Fats in Anemia Cases*
(The fat analyses are in percentages of the dried feces)

Case	Period	1 Total Fat	2 Neutral Fat	3 Free Acids	4 Soap Acids	5 Total Acids	Per Cent. Split	Per Cent. Utilized	Iodin Nos. for 1	Iodin Nos. for 2+3	Iodin Nos. for Food Fat
1. McG.	1	19.71	4.37	6.77	8.57	15.34	77.8	70.3	17.2	30.4	64.5
	2	21.05	5.09	7.06	8.90	15.96	71.1	73.2	18.6	32.3	64.5
	3	22.14*	7.57	4.61	9.88	14.57	65.8	....	....	30.6	.
2. M'd.	1	33.69	13.47	12.00	8.22	20.22	60.0	72.3	13.82	18.3	68.9
	2	31.54	10.28	14.13	7.13	21.26	67.4	78.2	18.1	26.0	69.9
4. Mat.	1	26.62	15.97	5.08	5.57	10.65	40.0	80.0	4.0	5.1	60.9
	2	24.86	15.05	6.43	3.38	9.81	39.5	73.0	....	24.4	60.9
5. Bgh.	1	21.04	10.33	3.95	6.79	10.74	50.9	79.2	....	33.6	60.9
8. Dug.	1	21.4	13.5	4.0	3.9	7.9	36.9	82.8			
	2†	23.9	14.8	5.7	3.4	9.1	38.0	88.7			
9. Mill.	1	29.1	14.3	12.3	2.5	14.8	50.7	84.4			
	2†	32.2	16.9	12.1	3.2	15.3	47.2	83.4			
10. Sch.	4	22.6	7.2	8.4	7.0	15.4	68.1	83.5			
	5†	28.0	11.0	12.0	5.8	17.8	63.5	88.5			
12. Boy.	1	17.78	13.06	3.00	1.72	4.72	26.5	76.9	30.67	33.9	60.9
13. Cook. ..	1	14.90	6.80	4.65	3.44	8.09	54.3	88.3	....	40.4	60.9
	2	16.92	10.92	3.10	2.90	6.00	35.5	87.8	....	40.6	60.9
14. Hel.	3	17.63	14.21	2.08	1.37	3.40	19.4	89.0	....	35.9	60.9
15. Plom. ..	1	24.3	13.0	5.9	6.4	12.2	50.3	77.4			

* Fat extractions made on the fresh stool.
† The fat ingestion was doubled in these periods over the preceding periods.

in the Orient. According to Castellani and Chalmers,[43] beriberi shows a certain degree of anemia, with leukopenia and a diminished number of polymorphonuclear leukocytes. Again, secondary anemia may occur in infantile scurvy (Hess [44]), in pellagra (Hillman [45]), as the result of

42. Fayrer, J.: Beriberi, Quain's Dictionary Medicine, London, 1888, p. 104.
43. Castellani, A., and Chalmers, A. J.: Beri-beri and Epidemic Dropsy, Manual of Tropical Medicine: New York, Wm. Wood & Co.. Ed. 3, 1919, pp. 1686-1687.
44. Hess, A. F.: Infantile Scurvy: the Blood Vessels and the Diet, Am. J. Dis. Child. **8**:385-405, 1914.
45. Hillman, O. S.: Some Hematologic Findings in Pellagra, Am. J. M. Sc. **145**:507-513, 1913.

continued reduced diets (Benedict [46]), and in rice fed rabbits (Downs and Eddy [47]). As yet we have little information as to whether or not vitamins play any part in hematogenesis. Vitamin deficiency may well be a predisposing factor for the acute exacerbation and may delay the onset and progress of the remissions in pernicious anemia.

For the limited number of cases reported here in which we have given adequate and iron rich diets, we have found little difficulty in establishing favorable iron balances along with clinical improvement and lessened recourse to transfusion. Our results would tend to confirm those of Whipple and his associates,[48] who found that in experimental hemorrhagic anemia in dogs, blood regeneration is hastened on a diet containing meat, liver, or other iron rich foods. However, Musser [49] has found that his dogs rendered anemic by repeated small bleedings were not so amenable to a high iron diet; he frankly admits that the factor of damaged blood formation in the clinical anemias of man was not of course present in either Whipple's or his own dogs. We realize that caution must be exercised in concluding from our few cases that an iron rich diet hastens blood regeneration in pernicious anemia where spontaneous remissions may occur. And while we may suggest that every effort should be made to have the patients consume such a diet in the hospital and that they should receive instructions as to diet when discharged, we still feel justified in continuing the administration of iron in the form of Blaud's pills and arsenic as Fowler's solution.

SUMMARY

Eleven cases of pernicious anemia, and for comparative data, one case each of an aplastic anemia, pregnancy anemia, hemolytic icterus and splenic anemia, have been studied.

Low whole blood and plasma fats were found in the severe pernicious anemia cases and tended to increase with improvement in the blood picture for the individual cases. The low blood fats seem to be associated with higher iodin numbers (by a micro-adaptation of the Hanus method) though the amounts of the unsaturated fatty acid groups as evidenced by the total iodin absorbed are not excessive. An increased

46. Benedict, F. G., et al.: Human Vitality and Efficiency Under Prolonged Restricted Diet, Washington, Carnegie Inst., 1919, Pub. No. 280.

47. Downs, A. W., and Eddy, N. B.: Secretin: V. Its Effects in Anemia, Am. J. Physiol. **58**:296-300, 1921.

48. Whipple, G. H.; Robscheit, F. S., and Hooper, C. W.: Blood Regeneration Following Simple Anemia. IV. Influence of Meat, Liver and Various Extractives Alone or Combined with Standard Diets, Am. J. Physiol. **53**: 236-262, 1920.

49. Musser, J. H., Jr.: The Influence of Inorganic Iron on the Regeneration of Blood After Hemorrhagic Anemia, Arch. Int. Med. **28**:638-648 (Nov.) 1921.

unsaturated fatty acid content, therefore, should not be a factor for hemolysis in pernicious anemia.

That blood and plasma cholesterol figures are low in pernicious anemia cases and increase as the blood is regenerated is confirmed. Low figures were found also for one splenic anemia case.

More favorable nitrogen and especially iron balances may be readily established in pernicious anemia and some other anemias (excepting iron in our case of splenic anemia) when diets rich in food iron (Whipple) and comparatively low in calorie and protein values are given. Negative nitrogen balances and coincident iron retention may obtain.

Characteristic but not constant alterations in the nitrogen partition in pernicious anemia are low urea and moderate ammonia nitrogens, and high uric acid figures. The immediate effects of blood transfusions on the daily nitrogen partition (two cases) are an increase in the total, urea, uric acid, and creatinine nitrogen elimination, persisting over at least two days.

A fat utilization of from 72 to 89 per cent. in our pernicious anemia cases is quite satisfactory when the low fat of the diet is considered. Our data furnish no evidence of the intestinal formation of fatty acids of high iodin absorption values.

In view of our experience, the use of iron-rich and vitamin adequate diets in the anemias is urged, but we do not feel that established therapeutic measures to promote hematogenesis should be neglected.

BLOOD PRESSURES IN FIFTEEN THOUSAND UNIVERSITY FRESHMEN *

WALTER C. ALVAREZ, M.D.

Assisted by

ROSALIND WULZEN AND LUCILLE J. MAHONEY

SAN FRANCISCO

About two years ago one of us (WCA) published a number of observations based on a statistical study of nearly 9,000 blood pressure records made on the incoming freshmen at the Students'Infirmary of the University of California.[1] That analysis led to a number of conclusions which were so surprising and so contrary to all previous teachings that the need was felt for further study with a larger series of data. In the first place, it was found that hypertension is not a disease of old age alone; it is found commonly among young people, healthy enough to go to college. Furthermore, the pressure does not increase with age as we have always thought. The average actually drops from the age of 17 to 21 in the men, and from 17 to 25 in women. After that, it stays about the same among the men until after 50; among the women it rises quite rapidly after 25, and very rapidly after 40. The result is that although the young women's pressures average 10 mm. or more below the young men's, after 45, so far as our data go, the women actually average higher than the men. It is interesting also to note the marked difference between the amount of hypertension among the girls and boys. It appears earlier in the boys and is often quite high. Thus, one 18 year old boy was found with a pressure exceeding 215 mm.

It was hard to believe at first that there could be so much hypertension among presumably healthy young men, but a comparison of our data with some data obtained by Barach and Marks, Lee, some of the insurance examiners, and some of the army physicians showed that very similar observations had been made elsewhere.[1]

A careful statistical analysis of the figures showed that those for the women were probably quite accurate and trustworthy; their distribution curves were fairly smooth, and the yearly averages for the 1919 freshmen were almost identical with those for the 1918 freshmen.[2]

The figures for the men were not so satisfactory, partly because the examiners showed a strong tendency to read to the nearest multiple

* From the George Williams Hooper Foundation for Medical Research, University of California Medical School and the University Infirmary.

1. Alvarez: Arch. Int. Med. **26**:381 (Sept.) 1920.

2. A few of the data classed under the heading 1918 were secured in 1916 and 1917.

TABLE 1.—*Blood Pressure Observations on Men Students*

Pressure	Ages													Total	Per-centage	Per-centage	Percent-ages Smoothed	Pressure
	16	17	18	19	20	21	22	23	24	25 to 26	27 to 30	31 to 35	36 to 40					
85- 89	.....	1	3	.....	.....	.....	.....	.....	.....	1	.....	.....	.....	5	0.08	0.08	0.15	85- 89
90- 94	.....	1	2	3	4	4	1	.....	.....	.....	3	.....	.....	18	0.30	0.38	0.36	90- 94
95- 99	1	2	3	13	3	10	.....	2	.....	2	.....	2	.....	38	0.64	1.02	0.82	95- 99
100-104	1	3	14	21	11	13	10	5	3	2	5	1	.....	89	1.48	2.50	1.44	100-104
105-109	1	11	17	16	20	15	6	6	5	5	8	3	9	122	2.03	4.53	3.65	105-109
110-114	6	40	79	87	41	52	36	26	18	29	17	12	4	447	7.45	11.98	7.15	110-114
115-119	9	49	116	106	78	59	47	37	26	36	36	18	6	622	10.37	22.35	12.50	115-119
120-124	21	97	249	204	143	136	89	64	47	59	49	23	15	1,196	19.96	42.31	14.45	120-124
125-129	9	57	124	125	69	66	49	49	20	36	26	14	6	650	10.85	53.16	14.60	125-129
130-134	17	103	232	190	156	106	65	57	45	60	34	28	11	1,104	18.41	71.57	13.60	130-134
135-139	9	57	100	84	49	43	33	22	20	19	12	10	6	464	7.74	79.31	10.48	135-139
140-144	11	54	122	115	83	59	43	34	22	23	21	11	7	605	10.08	89.39	7.85	140-144
145-149	3	27	44	30	26	12	12	4	7	3	7	3	1	179	2.98	92.37	4.81	145-149
150-154	3	15	57	44	23	22	17	11	9	8	4	2	3	218	3.63	96.00	3.24	150-154
155-159	.....	8	30	11	12	11	7	2	4	1	1	.....	.....	77	1.28	97.28	2.02	155-159
160-164	3	7	22	9	9	7	6	8	5	8	6	2	1	93	1.55	98.83	1.35	160-164
165-169	.....	3	4	3	8	5	1	2	.....	2	.....	1	.....	29	0.48	99.31	0.74	165-169
170-174	.....	4	5	3	5	.....	.....	3	.....	2	1	.....	.....	23	0.38	99.69	0.43	170-174
175-179	.....	1	1	1	1	1	.....	3	.....	.....	2	.....	.....	10	0.16	99.85	0.23	175-179
180-184	.....	1	1	1	.....	1	.....	.....	.....	3	.....	.....	.....	7	0.11	99.96	0.11	180-184
185-189	.....	.....	.....	.....	1	1	.....	.....	.....	.....	.....	.....	.....	2	0.02	99.98	0.01	185-189
190-194	.....	.....	.....	1	.....	.....	.....	.....	.....	.....	.....	.....	.....	1	0.01	99.99	0.01	190-194
195-199	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	195-199
200-204	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	200-204
205-209	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	205-209
210-214	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	210-214
215-219	.....	.....	1	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	1	0.01	100.00	0.01	215-219
Total	94	541	1,216	1,066	742	623	422	335	231	299	232	130	69	6,000				
Mean	129.3	130.1	130.0	128.2	129.5	127.6	128.3	129.1	129.0	128.3	127.0	127.0	126.7	128.9				
Standard deviation	12.5	13.2	13.4	13.0	13.6	13.8	12.8	13.9	12.6	14.1	14.0	12.2	12.8	13.5				
Standard deviation of the mean	1.29	0.57	0.38	0.40	0.50	0.55	0.62	0.76	0.83	0.81	0.92	1.07	1.54	0.17				
Probable error of the mean	0.87	0.38	0.25	0.27	0.33	0.37	0.42	0.51	0.56	0.54	0.62	0.72	1.04	0.12				
Median	128.5	129.0	129.0	127.4	129.0	125.6	126.3	126.8	128.0	126.2	124.0	126.5	124.0	127.6				
Mode (calculated)	126.9	126.8	127.0	125.8	128.0	121.6	122.3	122.9	126.0	122.0	118.0	125.5	118.6	124.7				
Coefficient of variation	9.7	10.1	10.3	10.1	10.5	10.8	10.0	10.7	10.6	11.0	11.0	9.6	10.1	10.5				
Measure of skewness	0.19	0.25	0.22	0.18	0.11	0.43	0.47	0.50	0.24	0.45	0.64	0.13	0.63	0.31				
Percentage over 130 mm.	49	52	50	46	50	43	43	43	48	43	38	44	42	47				
Percentage over 140 mm.	21	22	23	20	22	19	20	20	20	17	18	14	17	20				

TABLE 2.—*Blood Pressure Observations on Women Students*

Pressure	Ages													Total	Per-centage	Per-centage	Percent-ages Smoothed	Pressure
	16	17	18	19	20	21	22	23	24	25 to 26	27 to 30	31 to 35	36 to 40					
80- 84	1	.....	2	.....	.....	1	1	.....	.....	.....	1	.....	.....	6	0.06	0.06	0.06	80- 84
85- 89	.....	.....	4	5	2	2	.....	2	1	2	2	.....	.....	20	0.22	0.28	0.22	85- 89
90- 94	1	7	20	15	7	3	4	5	2	2	1	.....	.....	67	0.75	1.03	0.75	90- 94
95- 99	6	30	40	31	18	19	17	11	9	10	14	8	8	221	2.47	3.50	2.47	95- 99
100-104	12	72	158	117	72	53	48	40	20	45	51	30	25	743	8.24	11.74	8.24	100-104
105-109	22	92	166	145	83	73	46	43	29	57	69	45	20	870	9.75	21.49	12.99	105-109
110-114	29	186	431	318	187	107	88	70	84	88	109	84	31	1,872	20.98	42.47	16.47	110-114
115-119	25	154	285	221	102	106	68	63	57	74	79	57	28	1,379	15.45	57.92	17.21	115-119
120-124	41	210	379	319	175	141	79	78	44	70	98	81	43	1,758	19.70	77.62	15.48	120-124
125-129	18	100	206	152	84	59	41	40	20	25	51	25	25	855	9.57	87.19	10.80	125-129
130-134	17	88	151	97	58	49	35	13	25	28	44	36	14	655	7.35	94.54	6.95	130-134
135-139	10	25	64	42	24	15	12	8	4	8	8	14	8	242	2.72	97.26	3.82	135-139
140-144	3	21	36	23	16	6	7	9	2	5	4	15	12	159	1.79	99.05	2.01	140-144
145-149	.....	5	9	7	4	4	1	1	1	.....	.....	2	2	36	0.40	99.45	0.91	145-149
150-154	.....	2	4	5	3	3	.....	3	.....	1	2	2	5	30	0.33	99.78	0.45	150-154
155-159	.....	2	2	1	.....	.....	.....	1	1	2	1	.....	2	12	0.13	99.91	0.20	155-159
160-164	.....	1	1	.....	.....	.....	.....	.....	.....	.....	.....	.....	1	3	0.03	99.94	0.03	160-164
165-169	.....	.....	1	.....	.....	.....	.....	.....	.....	.....	.....	.....	1	2	0.02	99.96	0.02	165-169
170-174	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	1	.....	.....	1	0.01	99.97	0.01	170-174
175-179	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	1	.....	.....	1	0.01	99.98	0.01	175-179
180-184	.....	.....	1	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	1	0.01	99.99	0.01	180-184
185-189	.....	.....	1	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	1	0.01	100.00	0.01	185-189
Total	185	1,004	1,961	1,498	895	701	447	387	299	397	536	399	225	8,934				
Mean	118.0	118.1	117.7	117.3	117.2	116.7	116.3	116.4	116.1	116.1	116.6	118.2	120.0	117.3				
Standard deviation	10.9	10.7	11.0	10.4	10.3	10.1	10.7	11.1	9.8	10.5	11.0	10.9	13.7	10.8				
Standard deviation of the mean	0.80	0.34	0.25	0.27	0.34	0.38	0.50	0.57	0.57	0.53	0.48	0.55	0.90	0.11				
Probable error of the mean	0.50	0.23	0.17	0.18	0.23	0.25	0.33	0.38	0.38	0.35	0.32	0.37	0.60	0.08				
Median	118.0	117.7	116.8	116.7	116.4	115.5	115.4	115.7	114.4	115.0	115.3	116.8	119.0	116.4				
Mode (calculated)	118.0	116.9	115.0	115.5	114.8	113.1	113.6	114.3	111.0	112.8	112.7	114.0	117.0	114.6				
Coefficient of variation	9.2	9.1	9.4	8.9	8.8	8.7	9.2	9.5	8.4	9.0	9.4	9.2	11.4	9.2				
Measure of skewness	0.0	0.11	0.25	0.17	0.23	0.36	0.25	0.19	0.52	0.31	0.35	0.39	0.22	0.25				
Percentage over 130 mm	16	14	13	11	11	11	12	9	11	11	11	17	22	13				
Percentage over 140 mm	1.6	3.0	2.8	2.4	2.5	1.8	1.8	3.6	1.3	2.0	1.6	4.7	10	2.7				

of ten on the scale, but mainly because there was a large difference between the yearly averages in 1918 and 1919. Thus the arithmetical mean (average) for the 1918 men between the ages of 17 and 19 inclusive was 122 mm.; for the 1919 men it was 131 mm. Naturally, it was highly desirable to see which of these two averages was the more nearly correct, and the only way in which this could be done was to secure more data. It was feared also that the sampling from the male community had been affected in some way by the war which drew on the physically fit and left the unfit.

In an attempt to clear up this problem and to obtain accurate standards of blood pressure, we have secured data on 3,070 more men and 3,127 more women—freshmen entering during 1920 and

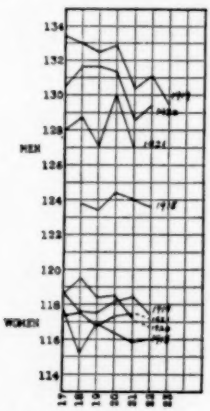


Fig. 1.—Averages of data on blood pressure in university freshmen secured during the years 1918 to 1921.

1921. We now have figures on 6,000 men and 8,934 women, or 14,934 in all. Their distribution is shown in detail in Tables 1 and 2.[3]

3. The averages have been obtained with the help of a short cut method described by Rugg (Statistical Methods Applied to Education, Cambridge, Mass., Houghton, Mifflin Co., 1917). As this method is based on the assumption that the data are evenly distributed in each group of five figures (85-89; 90-94, etc.), the results obtained vary a little from those given in the previous paper. Those were based on the individual figures which, as we have noted above, were grouped largely around the multiples of ten on the scale. If the examiners had been more careful in avoiding this tendency, the data would have been distributed evenly, and the averages would probably have been very close to those we have now obtained.

The palpatory method was used in taking the pressures. The men take a tepid shower before the examination, and are examined in the reclining position. They are more likely to stand around in negligée and get cold than are the women. The women's pressures are taken standing. One large aneroid and three mercury instruments were used.

DIFFERENCES IN THE AVERAGES FOR FOUR DIFFERENT COLLEGE YEARS

The arithmetical means or "averages" for the data secured year by year have been plotted in Figure 1. As averages based on data from groups smaller than 100 have large possibilities of error, they have been omitted from the graphs. The figure shows the close agreement of the four sets of data from the women; nearly all of which fall within the limits of error determined by the sizes of the groups. We see also the wide divergence of the averages for the men; wider than we would expect from the limitations of the method and the smallness of the groups. (The "probable error" for these averages is actually about $\pm$ 0.6 mm.). The 1918 averages are in a class somewhat by themselves, but it will be noted that the average pressure has fallen steadily since 1919, so that the figures for 1921 are not much above those of 1918. The possible significance of these findings will be discussed later.

MEASURES OF CENTRAL TENDENCY

Let us now turn back again to Tables 1 and 2 to see what we are going to do with the figures recorded there. They range from 85 to 219 mm. for the men, and from 80 to 189 mm. for the women. The first question that will arise in the mind of a practicing physician is: What are the dividing lines between normal and abnormal? What should be the blood pressure of a healthy young man or woman? Ordinarily, we take the average of all the data as the central point of normality, but it can easily be seen that in the usual mixture of normal and diseased people, there should really be two averages—one for the healthy and one for the diseased. If we average the two groups together, we get a figure which is too high for the normals and too low for the diseased. In this study we see that a number of the averages for the 1919 men exceed 130 mm.; and yet, clinically, we know that pressures above 130 in young men are very likely to be accompanied sooner or later by symptoms of hypertension or mild cardiovascular-renal disease. Hence, in this case, we can hardly use the arithmetical mean as a standard of normality.

The median is another figure expressing central tendency. It represents the middle number in the series, on either side of which lie 50 per cent. of the data. It is not influenced quite so much by groups of data at the two ends of the distribution, but it still is affected by them a good deal.

In many ways the mode seems to be the most suitable measure for our purposes. It is the value on the scale which occurs most frequently and typically, hence, it forms the apex of the distribution curve (Fig. 2). In a perfectly symmetrical curve it coincides with

the mean and the median, but when the curve is "skewed" the mode remains behind while the mean is pulled over by the large number of data from those persons who are abnormal. The mode can be determined roughly by inspection of the "smoothed" distribution curves, or it may be calculated by Pearson's method.[4] The modes charted in

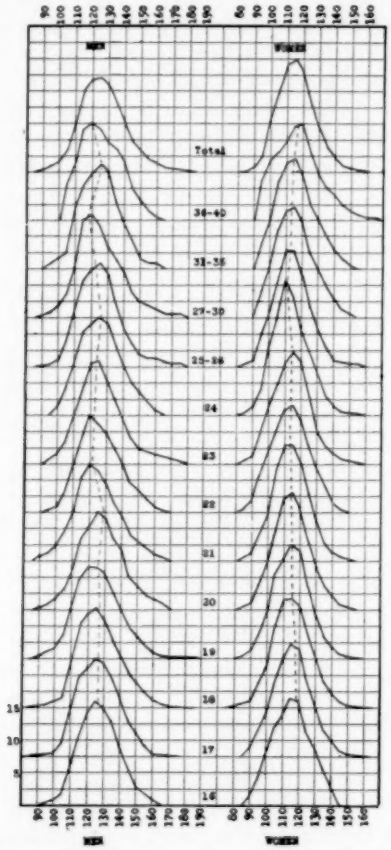


Fig. 2.—Blood pressure in university freshmen.

4. It is hard to know, in writing a paper like this, how far to go in the matter of explaining the terms and methods used in statistical work. Naturally, in the space of a short article, nothing adequate can be given; and the reader who remains puzzled must be asked to turn to the books by Rugg, Whipple (Vital Statistics, New York, John Wiley & Sons, 1919) or Thorndike (Introduction to the Theory of Mental and Social Measurements, New York, 1916). It is unfortunate that few research workers in medicine are ever given that training in statistical methods which would enable them to analyze and to evaluate quickly and correctly the data with which they are constantly dealing.

Figures 2 and 3 have been calculated, and it will be seen that they correspond pretty closely with the peaks of the curves.

It is clear from Figure 3 that the mode for the men drops from 127 mm. at the age of 16, to 118 mm. at the age of 30. The mode for the women drops from 118 mm. at the age of 16, to 111 mm. at the age of 24; and after that rises quite rapidly. The mode for all the men was 124.7 mm., and for all the women, was 114.6 mm. These figures, we believe, represent the best standards of normal now available. Unfortunately they represent almost the only standards, because, as pointed out in the previous article,[1] most of the figures published hitherto have been obtained from the study of picked groups of accepted insurance applicants or accepted recruits. Very few attempts have been made to

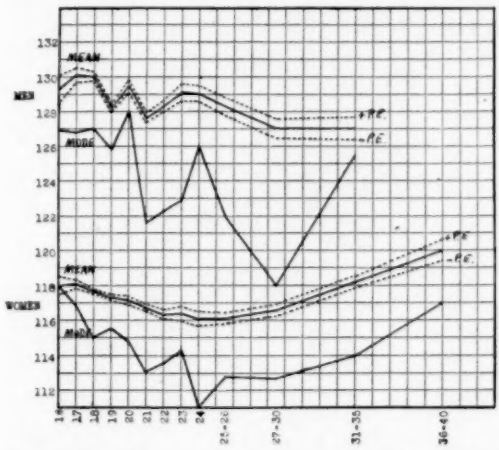


Fig. 3.—Mode and mean blood pressure in university freshmen.

get a fair sampling from the community as a whole. As was argued in the preceding paper,[1] the students in a free university probably represent a good sampling from at least the more intelligent part of the community.

The mean for the women drops very definitely from the age of 17 to 25; and for the men, there is a similar but more uneven drop from 17 to 35. This drop is not quite so marked as that which we have just noted in the curves for the mode.

IRREGULARITIES IN THE CURVES

It is hard to uderstand why the curves for the mean and the mode of the men should be so irregular in places. As will be seen from the location of the dotted lines, which represent the limits of the probable

error of the mean, the deflections about the age of 20 exceed that error; and, in fact, they almost exceed ± 3 times the standard deviation of the mean. As that range should include 99.73 per cent. of the data in a distribution curve, the chances are 9,973 to 27, or 368 to 1, that these deflections are not due to accident but that they mean something This conviction is strengthened when we turn to Figure 1 where we see that the rise from ages 19 to 20 is found on three out of four of the

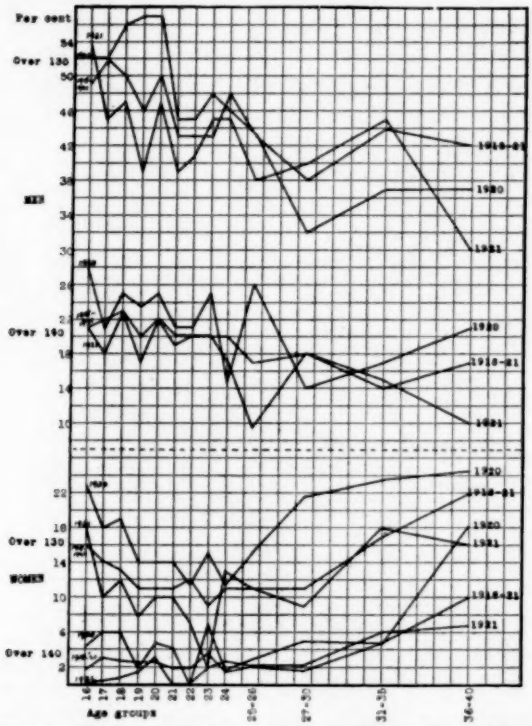


Fig. 4.—Percentage of blood pressure above 130 and 140 mm.

yearly graphs, and the drop from 20 to 21 is definite in all of them. It is strengthened, also, when we note that there are corresponding upward swings in the graph for the mode; and in Figure 2, there are corresponding shifts to the right of the distribution curves.

It would seem, then, that during these years there must be some rhythmic upward tendency in the mechanism which regulates blood pressure. The hard thing to understand is how enough of these yearly tendencies can be in step to affect the curves, because we know that in children there often are big differences between the calendar age and

the developmental age. Such differences in these youths might permit the appearance of broad, rounded rises like the rise in the curve for the men about the ages of 23 and 24, but it is hard to see how they could permit the appearance of a sharp rise like that at the age of 20. Any overlapping of ups and downs would tend to produce a straight line at that point. It is interesting that the women's curves for mean and mode show slight upward tendencies between 19 and 20 and at 23, which, perhaps, correspond to those of the men. These peculiarities, naturally, can be given significance only if they appear again in the same places in curves drawn from data secured by other workers. For the present, they can serve only to make us ask questions.

PERCENTAGE OF HYPERTENSION

Figure 4, showing the percentage of the data above 130 and 140 mm. is interesting as it shows the peculiar yearly variations, and also the

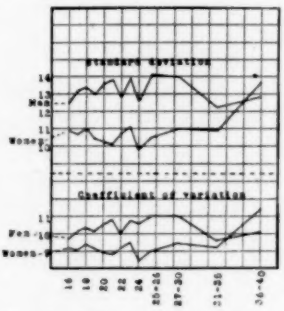


Fig. 5.—Changes according to age.

same general tendencies from the ages of 16 to 40 that we have noted in the curves for the mean and mode. As was pointed out in the previous paper,[1] most writers are agreed that a pressure exceeding 140 in a young person is abnormal, and some are coming to the point where they are willing to place the limits at 130 mm. Here we find from 18 to 26 per cent. of the boys with pressures exceeding 140, and from 35 to 57 per cent. with pressures exceeding 130 mm. Among the younger women, about 3 per cent. have pressures exceeding 140, and 21 per cent. have pressures exceeding 130 mm. The remarkable thing is the steady decrease in the incidence of hypertension in the men as they grow older. The question arises: Do their individual pressures decrease, or do many of those persons with high pressures in boyhood drop by the wayside as they grow older? That can only be answered by watching a number of these men for a long period of time.

MEASURES OF VARIABILITY

Figure 5 shows the yearly changes in the standard deviation and in the coefficient of variation. The standard deviation is the square root of the average of the squares of the deviations from the average of the whole distribution. It is a valuable measure of the variability, and naturally is greater here for the men than for the women. It is interesting to note that the women's pressures are more variable than the men's after the age of 38 or 40.

The coefficient of variation is another measure of the variability, and its graph is naturally very similar to that of the standard deviation. It represents a ratio between the standard deviation and the average from which the deviations were taken.

The measure of skewness which will be noted in Tables 1 and 2 is the one suggested by Pearson. It is obtained by dividing the difference between the mean and the mode by the standard deviation. In both men and women it increases from 16 to 30, after which, perhaps on account of the smallness of the groups, it varies widely up and down.

DISCUSSION

Unfortunately, the first object of this paper, that of establishing normal standards of blood pressure for young men, has not been accomplished to our entire satisfaction. The new data still show a lack of homogeneity which is disturbing. In attempting to explain these big differences in the measurements made in the four years from 1918 to 1921, we might blame the instruments, the examiners, the sampling, the war, and, perhaps, the influenza epidemic. Errors due to the instruments can probably be excluded as three out of four were mercury manometers and the aneroid was checked from time to time. Furthermore, instruments were exchanged back and forth with the women's department where no such wide variations were observed. Similarly, we can probably exclude errors due to differences in the personal equations of the examiners in the different years. Each year the examining staff consisted of four men and from five to seven women. Of the men, only one remained during the four years; usually there were two hold-overs and two new workers. Among the women, in 1919 there were two hold-overs and three new workers; in 1920 there were four hold-overs and one new worker, and in 1921 there were three hold-overs and four new workers. Any individual differences which may have existed in the readings of the women examiners must have balanced one another because we have seen that the data secured by them year by year are quite uniform. The presumption is, then, that the personal equations of the men also should have balanced one another so as to have become negligible.

The next question is: Was the sampling affected by the war? In the previous paper it was assumed that the drafting away of the physically fit into the army and navy might have left behind a larger percentage of militarily unfit who might, presumably, have shown a larger incidence of hypertension. On looking up the figures in the recorder's office we find, however, that the men had already gotten back in large numbers in the college year of 1918-1919 (Table 3). Furthermore, most of the freshmen were under draft age. It is hard to say, therefore, just how the war affected the pressures if it did so at all.

TABLE 3.—*Men Entering the University of California in 1915 to 1921, Inclusive*

	Number
1915-16	914
1916-17	1,019
1917-18	847
1918-19	1,531
1919-20	1,782
1920-21	1,571
1921-22	1,364

The strange thing is that the pressures should be so low in 1918; that they should take a big jump in 1919, and should then gradually return in 1920 and 1921 toward the original figures. The fact that the women's pressures follow a rather similar course suggests strongly that we have here a manifestation of some influence affecting both men and women during these years (Table 4). There immediately comes to mind the suggestion that the influenza epidemic which must

TABLE 4.—*Blood Pressure Averages for the Data Collected Year by Year*

	Men	Women
1918	123.9	116.3
1919	131.8	118.0
1920	130.6	118.5
1921	128.1	117.3

have attacked many of those registering in 1918-1919, could easily account for the low pressures obtained in that year. It is not so easy, however, to explain the big rise in the following two years. Another solution of the problem would be to say that there are yearly variations in the average human blood pressure, and that a low ebb in 1918 predisposed us to a serious epidemic. Naturally, with only four years' data to go on, and other possible explanations for the discrepancies in sight, this solution cannot be taken seriously, but it might be kept in mind by those who have opportunity to gather similar data in the future.

Another disturbing observation is that the averages even for the 1918 men are considerably higher than those obtained on several hundred

high school boys of corresponding ages in San Francisco. The averages for the high school girls are practically the same as those for the college women. However, as will be seen from Table 5, the range for the boys is much greater than that for the girls, and it increases steadily from the age of 14 to the age of 16. The standard deviation for the 16 year old girls was 9.3 mm. and for the 16 year old boys it was 12.9 mm. These figures agree closely with those obtained at the University. Moreover, it will be noted that hypertension is found commonly among the school boys. One of us (WCA) checked a number of the readings on these boys and found them correct.

HIGH BLOOD PRESSURE AND SEX

The study of the new 1920 and 1921 data amply confirms the conclusions drawn in the previous paper. Certainly it would seem that

TABLE 5.—*Blood Pressures of High School Boys and Girls in San Francisco*

Pressures	Boys: Aged			Girls: Aged		
	14	15	16	14	15	16
85- 89	..	..	..	..	..	1
90- 94	4	2	..	..	1	..
95- 99	6	7	4	..	2	..
100-104	11	18	6	3	7	9
105-109	13	12	14	3	9	11
110-114	19	21	19	6	17	10
115-119	10	18	17	7	15	15
120-124	15	18	30	15	36	26
125-129	4	11	11	10	20	19
130-134	4	14	13	5	11	7
135-139	4	6	5	4	10	6
140-144	3	7	7	..	..	1
145-149	..	1	1	..	1	..
150-154	..	5	3	..	..	..
155-159	..	..	1	..	..	..
160-164	..	..	1	..	..	..
165-169	..	..	..	..	..	..
170-174	..	..	..	..	..	1
Total	93	140	132	58	129	106
Mean	110.2	118.6	121.2	121.2	120.4	119.8

high blood pressure can hardly be due, as many have thought, to focal infections or to the strenuous life. Otherwise there could not be such marked sexual differences and so high an incidence in youth. Unfortunately, these data do not extend quite far enough to take in the periods of puberty and the menopause. It is highly desirable that such data be secured, because undoubtedly they will throw much light on the nature of high blood pressure.

Since the previous paper was published there has appeared an article by Faber and James on the blood pressures in normal children.[5] Unfortunately, they studied only 651 boys and 450 girls so that the age groups are too small for accurate work. They found the average

5. Faber and James: Am. J. Dis. Child. **22**:7 (July) 1921.

systolic pressure about the same for boys and girls, rising from 89 mm. at the age of 3, to 115 mm. at the age of 16. They found a greater variability among the girls than among the boys, which is just the reverse of what is found after 16. They noticed a marked variability in the diastolic pressures of the girls after 13, a change which was not present among the boys. Similarly, Burlage [6] found, in studying 1,700 girls and young women, a rapid rise in the systolic pressure from 104 mm. at 9 years to 124 mm. at 14 and 15. Then there was a rapid fall to about 114 at the age of 18. After that the pressures were quite constant up to 26 years. Although he used the auscultation method his results agree fairly well with ours.

It is interesting to note that the influence of sex is hardly recognizable in childhood; that it becomes exaggerated about the age of puberty and again in women about the menopause. It is suggestive also that in young women there seems to be a high degree of correlation between the incidence of hypertension and the presence of the various symptoms and signs of ovarian hypofunction. It would seem that the internal secretion of the ovary is able in some way to suppress the tendency to hypertension which many of the girls presumably inherit equally with the men.

This point may, perhaps, be made clearer if we turn to some experimental work done recently on fowls. Goodale [7] showed several years ago that in ducks and hens the extirpation of the ovaries will lead to the assumption by the female of a male type of plumage. Apparently, some substance secreted by the ovary is able to restrain or suppress the male characteristics, and the work of Boring, Pearl and Morgan [8] suggests strongly that it arises in the lutear or yellow pigment containing cells of that organ. Such cells have not been found in the testicles of adult fowls, except in the case of the Seabright bantam and some Campines, where the males are so hen feathered that they are hard to tell from the females. As was to be expected from the theory, when these males were castrated, they developed plumage resembling that of the males of other breeds. The ordinary male fowls, when castrated, retain a male type of feathering.

It has been known for many years that old hens, or hens with diseased ovaries will often develop male characteristics; and similarly, women with undeveloped or diseased ovaries not infrequently show a male distribution of body hair on the abdomen, breasts, and face. It is suggestive that the giving of corpus luteum to many of these women seems to have a restraining influence on the development of their hyper-

6. Burlage: Proc. Soc. Exper. Biol. & Med. **19**:247, 1922.
7. Goodale: Biol. Bull. **20**:35, 1910; Amer. Naturalist **47**:159, 1913.
8. Boring and Pearl: Anat. Rec. **13**:253, 1917. Pearl and Boring; Am. J. Anat. **23**:1, 1918. Boring and Morgan: J. Gen. Physiol. **1**:127, 1919.

tention. If our reasoning is at all correct, it might be worth while to try ovarian extracts also on men with high blood pressure. Another suggestion comes from the work of Torrey and Horning [9] who found that the giving of dried thyroid to normal male Rhode Island Red chicks causes them to develop hen feathering. As this does not take place in castrated males, the assumption is that the thyroid extract probably stimulated the function of the few lutear cells which are known to be present in the testicles of very young males.

SUMMARY

An analysis has been made of the systolic blood pressures of 6,000 men and 8,934 women—freshmen entering the University of California.

The pressures of the women are more uniform than those of the men, and they average 11 mm. lower.

Hypertension is very common among the younger men, about 45 per cent. having pressures exceeding 130, and 22 per cent. having pressures exceeding 140 mm. Among the women, about 12 per cent. had pressures exceeding 130, and about 2 per cent. had pressures exceeding 140 mm. Strange to say, the average pressure for both men and women drops gradually during the first years of adult life.

The pressures for the men are grouped mainly about 127 mm. at the age of 16, and about 118 mm. at the age of 30.

The pressures for the women are grouped about 118 mm. at the age of 16; about 111 mm. at 24, and about 117 mm. at 40.

Hypertension cannot be ascribed regularly to infections or to the strenuous life. It seems to be an inherited peculiarity the appearance of which can be suppressed in women so long as the ovaries function well.

---

9. Torrey and Horning: Proc. Soc. Exper. Biol. & Med. **19**:275, 1922.

BLOOD CONCENTRATION CHANGES IN EXTENSIVE SUPERFICIAL BURNS, AND THEIR SIGNIFICANCE FOR SYSTEMIC TREATMENT *

FRANK P. UNDERHILL, PH.D.,
GEORGE L. CARRINGTON, M.D., ROBERT KAPSINOW, M.D.,
AND
GEORGE T. PACK, M.D.

With the cooperation of

EPHRAIM SHORR, M.D., HENRY B. ROLLINS, M.D.,
FLORENCE I. PETERMAN, B.S., AND ALICE DIMICK, M.S.

NEW HAVEN, CONN.

In extensive superficial burns involving considerable areas of the body's surface a rapid concentration of the blood occurs, and in our opinion this hitherto unconsidered factor is of the greatest importance in the development of the syndrome characteristic of burns. Concentrated blood is a factor which cannot well be left out of consideration in the study of any diseased condition in which it manifests itself. Marked concentration of the blood means a failing circulation, an inefficient oxygen carrier, oxygen starvation of the tissues, fall of temperature, and finally, suspension of vital activities. This viewpoint was initiated during the World War by the results of an extensive investigation of the action of the lethal war gases [1] which produce a noteworthy concentration of the blood as a result of the acute massive edema. Similar conditions obtain in certain cases of influenza.[2]

On first consideration it may be difficult to correlate reactions in burns to those in war gas poisoning in such a manner that one underlying principle can be held responsible for the same ultimate condition in such widely differing abnormal states. Further reflection, however, will lead to the conception that in both pathologic conditions under discussion one fundamental fact stands out clearly—namely, that either detrimental agency leads to an extreme inflammatory reaction and destruction of tissue. This inflammatory reaction, whether in the case of war gas poisoning or in that of extensive superficial burns, meets a response on the part of the body. Fluid is poured out on the surface of the injured area. Up to a certain point the greater and more acute the inflammatory reaction the greater or more rapid will be the response. The acute edema of the lungs in war gas poisoning and in certain types

* From the Department of Pharmacology and Toxicology, Yale University, and the Section of Surgery, School of Medicine, Yale University.

1. Underhill: The Lethal War Gases, Yale University Press, 1920; Harvey Lectures, 1917-1919.

2. Underhill and Ringer: J. A. M. A. **75**:1531 (Dec. 4) 1920.

of influenza is readily explained in this manner. An extensive experience with burn cases enables us to assert that a similar rapid pouring out of fluid on the surface of the body occurs, or if the skin is intact the part affected becomes edematous with extreme celerity. The rapid and continued loss of fluid from the blood in burn cases quickly induces a marked concentration of the blood which becomes a factor of prime significance in the fate of the person concerned. It will readily be understood, of course, that other factors than blood concentration have their part in determining the outcome of superficial burns. Nevertheless, we are of the opinion that blood concentration is of extreme importance in any consideration relative to extensive superficial burns. It is a factor which contributes directly to the ultimate fate of the person suffering the injury.

The extent of concentration of the blood compatible with life depends in large measure on the interval during which concentrated blood is maintained. Previous experience would indicate that an animal or man cannot long survive blood concentrated 140 per cent. of the normal value. When concentration reaches 125 per cent. of the normal value, conditions for the maintenance of life are becoming precarious.

The recognition of blood concentration as a factor of importance leads to a rational method of treatment to control this factor. Rapid and continued introduction of fluid by all possible channels, as by mouth, by rectum, under the skin or intravenously will cause a gradual return of the blood concentration to normal and, in the investigation to be detailed later, a comparable improvement of systemic signs and symptoms. Forcing of fluid is certainly a logical procedure in burn cases, for not only will blood concentration be reduced to a normal level and thus tend to the maintenance of a normal circulation and heart action but any hypothetical poisons will be diluted sufficiently to diminish their degree of toxicity and this dilution will also undoubtedly greatly accelerate their elimination.

The experience with burn cases on which these views are based was gained as a result of observations carried through on twenty-one victims of a local theater fire. These patients were admitted to the surgical wards of the New Haven Hospital and through the courtesy of Dr. Samuel C. Harvey, surgeon-in-chief, and his staff, opportunity was afforded us to conduct the investigation. This communication is not concerned with the local treatment of the burned areas but is confined to the general condition and systemic treatment of the patients. It may be stated, however, that, in general, the local treatment consisted of paraffin film dressings with subsequent skin grafting when necessary.

Methods.—Changes in blood concentration were followed by analyses of the blood for hemoglobin according to the procedure of

Cohen and Smith. In the examination of the blood for the determination of nonprotein nitrogen, creatin, creatinin, glucose, urea and chlorids, the system of blood analysis advocated by Folin and Wu was followed.

The patients were admitted into the New Haven Hospital in the early evening of Nov. 27, 1921, and at once received first aid treatment and were sent to the various wards. In most instances some fluid was given at once, but systemic forcing of fluid was not begun until the following day. The patients naturally divided themselves into two groups: (*a*) those seriously burned, and (*b*) those not so seriously burned. Fluid was forced by mouth if possible. When this could not be done, fluid was introduced per rectum, under the skin, or in one case, in which all other methods failed, it was given intravenously.

TABLE 1.—*Classification of Burned Cases—Initial Values for Hemoglobin*

Group 1: Seriously Burned			Group 2: Less Seriously Burned		
Case Number	Hemoglobin		Case Number	Hemoglobin	
	In Percentage	In Percentage of Normal		In Percentage	In Percentage of Normal
1	174	(158)	16	129	(117)
2	230	(209)	17	150	(136)
3	200	(181)	18	130	(118)
4	167	(151)	19	129	(117)
5	167	(151)	20	135	(122)
6	167	(151)	21	130	(118)
7	153	(137)			
8	174	(158)			
9	170	(154)			
10	205	(186)			
11	164	(149)			
12	167	(151)			
13	200	(181)			
14	156	(138)			
15	167	(151)			

BLOOD CONCENTRATION IN EXTENSIVE SUPERFICIAL BURNS

For obvious reasons extensive observations on these patients were not made at once. At 3 p. m. of the day following the accident, hemoglobin estimations were first systematically carried out and continued for several subsequent days. On the basis of the clinical symptoms and the severity of the burns the patients may be divided into two groups, as shown in Table 1.

In the table of classification the initial figures for hemoglobin content are given and it is quite apparent that in extensive superficial burns the blood becomes markedly concentrated. Moreover, in the division of the more severely burned from those less severely burned there is a corresponding difference in the degree of blood concentration. In general, therefore, the more extensively burned patients responded with a greater concentration of the blood.

It is of interest to determine the approximate percentage increase of hemoglobin in order to learn the actual gravity of each case on the basis

that an increase of 40 per cent. of the normal value is incompatible with life if maintained for an extended period. Such figures may be found in brackets in Table 1. These figures are only approximate since 110 per cent. has been chosen as a result of experience for the normal value. Such a procedure is not exact since the normal hemoglobin value varies considerably in different subjects. It is, however, sufficiently accurate for the purpose stated. On this basis it is readily seen that all individuals in Group 1 had a blood concentration above the figure set as a dangerous level. It is also of interest to note that based entirely on clinical symptoms all of these patients, with the possible exception of two (Cases 12 and 14), were at once placed on the danger list. On the other hand, none of the cases in Group 2 were placed on the danger list and only one patient had a blood concentrated to the accepted danger point.

From such data, therefore, it seems conclusive that the determination of blood concentration in extensive superficial burns may serve as an index of the patient's general condition, and will indicate the extent to which fluid should be forced.

THE INFLUENCE OF FORCING FLUID ON THE HEMOGLOBIN CONTENT

The systemic treatment of these burn cases consisted simply in the forcing of fluids, water by mouth when possible, and the administration of small quantities of sodium bicarbonate. The quantity of fluid actually taken into the body varied for the individual patients, but, in general, from four to eight liters or more per day were given. In Table 2 may be found figures for hemoglobin during the period of observation, together with the ultimate fate of the case. From these data it may be seen that at first the hemoglobin figures fluctuate considerably, at times the blood concentration even exceeding the initial values. Such a variation may, perhaps, be taken as an indication of the unstable equilibrium of the water balance mechanism. It is quite possible that fluid under conditions of tissue desiccation is employed first of all in resaturating the dried tissues, and that fluid intake under these circumstances will not be evidenced in the blood by altered concentration until a certain water content of the tissues is reached.

Following the period of fluctuation of blood concentration there may be observed a steady fairly rapid fall in hemoglobin content. Coincident with this decrease in blood concentration, improvement in the patients' condition was observed. Those cases (Cases 3 and 10) that ended fatally as a result of the burns terminated either too rapidly for the forcing of fluid (Case 3) or else insufficient fluid was administered to change blood concentration significantly (Case 10). All the other patients recovered from the effects of the burns—although two

TABLE 2.—*The Influence of Forcing Fluid on Hemoglobin Content*

Date		Case Number																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
11/28/21	3 p. m.	174	230	200	167	167	167	153	174	170	205	164	167	200	156	167	129	150	130	129	135	130
	7 p. m.	197	214	...	...	161	159	150	200	174	208	161	167	167	130	130	120	136	114	129	120	120
	10 p m.	...	225	...	156	155	...	...	187	...	197	...	169	183				Removed	Removed			Removed
11/29/21	10 a. m.	174	194	Died	133	150	158	155	167	165	Died	161	172	188	153	144	143	to	to	127	122	to
	5 p. m.	165	214	...	122	149	144	156	183	156	...	161	142	176	128	133	136	home	home	138	125	home
	11 p. m.	...	...	...	...	...	...	...	...	...	...	...	...	153								
11/30/21	10 a. m.	149	156	...	120	138	139	135	143	139	...	152	130	153	136	120	126	...	...	139	128	
	5 p. m.	153	135	...	110	120	131	135	135	...	...	150	129	113	135	130	131	...	...	143	113	
	11 p. m.	...	...	...	...	...	...	...	...	...	...	...	...	128								
12/ 1/21	10 a. m.	143	126	...	113	123	134	127	127	135	...	133	126	123	119	95	122	...	...	139	117	
	5 p. m.	135	131	...	99	123	135	133	133	135	...	129	125	119	123	104	133	...	...	130	114	
12/ 2/21	10 a m.	122	132	...	101	112	123	119	126	125	...	123	143	109	120	103	130	...	...	120	Removed	
	5 p. m.	...	137	...	94	...	...	...	...	...	...	...	...								to home	
12/ 3/21	10 a. m.	131	133	...	98	122	115	133	139	126	...	125	119	120	114	94	136	...	...	180		
12/ 4/21	8 p m.	135	141	...	102	...	...	...	146	...	...	..	...	119	...	...	133					
12/ 5/21	10 a. m.	...	...	...	...	123	115	133	130	144	...	118	...	Died	109	...	126	...	...	110		
	2 p. m.	127	144	...	100	...	...	...	...	...	...	...	...	of pneumonia	...	92						
12/ 6/21	10 a. m.	128	123	...	94	130	117	123	120	136	...	125	113	...	115	...	125	...	...	128		
1/ 3/22		127	130	...	Died	Recov-	Recov-	Recov-	138	127	...	138	Recov-		Recov-	Recov-	Recov-			Recov-		
		Recov-	Recov-		later	ered	ered	ered	Recov-	Recov-		Recov-	ered		ered	ered	ered			ered		
		ered	ered		pneu-				ered	ered		ered										
					monia																	

deaths occurred later from pneumonia. The large percentage of recoveries is noteworthy in view of the severity of the burns suffered by the majority of the patients. As a result of our experience we are of the opinion that restoration of blood concentration to a normal level by introduction of fluid is of paramount importance in the systemic treatment of burned cases.

In order to bring out more clearly the changes in blood concentration as influenced by fluid administration, graphic illustrations are given in Charts 1, 2 and 3. All these instances were among the most serious cases. Inspection of these charts will reveal an apparent relationship between the diminution of blood concentration and fluid intake. In

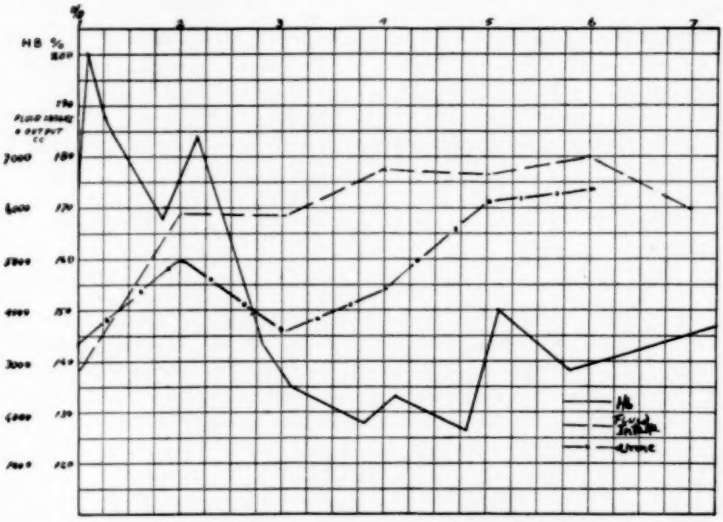


Chart 1.—The relation of blood concentration to fluid exchange (Case 8).

general, also, the urinary excretion follows a course similar to the intake but at a considerably lower level. Particular attention is called to Chart 3 since in this instance, owing to the impossibility of cooperation on the part of the patient and the failure of introducing sufficient fluid by rectum or subcutaneously, an intravenous infusion of salt solution was given. The result is obvious.

Although from the figures and other data relative to these observations one is apparently justified in concluding that restoration of blood concentration is of prime significance in burn cases, nevertheless, to the sceptically inclined there are at least two points at which the above conclusions may be attacked. In the first place, one may assume that fluid intake has only an inappreciable influence on blood concentration,

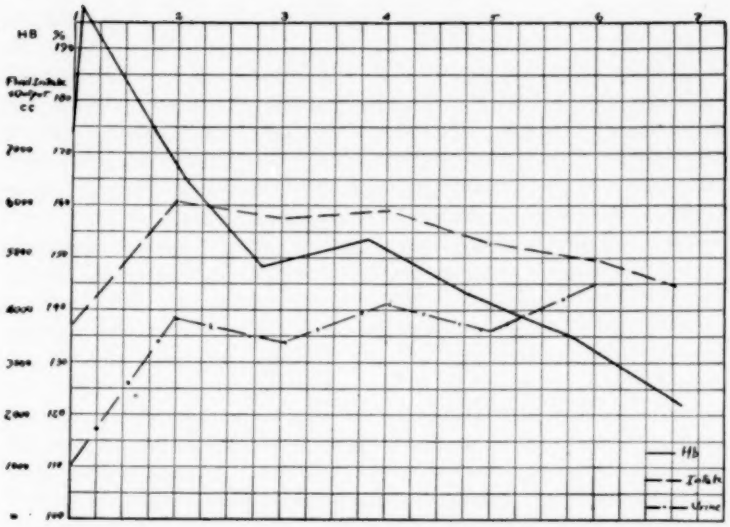


Chart 2.—The relation of blood concentration to fluid exchange (Case 1).

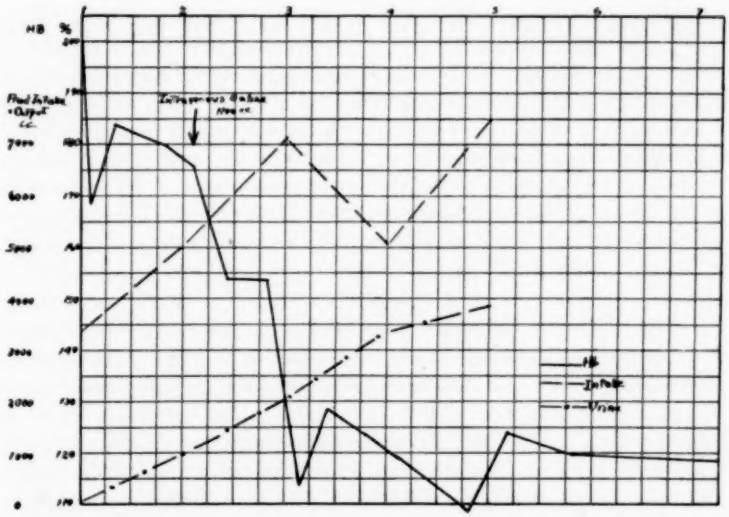


Chart 3.—The relation of blood concentration to fluid exchange (Case 13).

that fluid is excreted from the body almost as rapidly as it is ingested. All the available literature on the subject supports such an assumption. One point, however, must be emphasized, namely, that in nearly all instances in which this hypothesis has been put to the test the organism employed was that of a normal person. Herein lies the crux of the whole matter. It is utterly fallacious to predict the behavior toward water administration of an organism suffering from lack of water from observations made on an organism with a sufficiency of water supply. It is quite true that partaking of large volumes of water by normal man or dog does not perceptibly alter the concentration of the blood. So long as the water regulating mechanism of the body is normal such a result is to be expected. On the other hand, when an animal has been deprived of water for a sufficiently long period, blood concentration becomes markedly increased. Water administered under these circumstances causes a rapid fall in the concentration of the blood. The experiments by Keith [3] and by two of us (Underhill and Kapsinow [4]) cause us to reiterate the statement previously made that it is fallacious to draw conclusions relative to the abnormal organism when these inferences are largely based on observations on normal persons, and they furthermore dispose of one of the points of attack cited above.

A second point of attack centers in the query, "Did the fluid intake in these cases actually influence blood concentration or would blood concentration have returned to the normal without such aid?" To answer this question absolutely control experiments would be necessary. Such a control, however, is obviously lacking. The question receives a partial answer from the experiments of Keith and our own cited above together with our experience with war gas poisoning. Death may follow, but blood concentration is not restored to near normal limits under conditions of water lack unless sufficient fluid has been introduced. We believe, however, that the question is fully answered by our experience with one burned patient treated outside the hospital. A victim of the same fire, this patient was cared for at his home by his own physician. Special attention to forcing of fluids was lacking. This case was especially badly burned and presented the typical signs and symptoms characteristic of intoxication from burns, chief among which was an active delirium, it being necessary to take measures to keep the patient in bed. This was succeeded by a period of collapse and unconsciousness, death being anticipated. After a period of eight days, consultation with the physician resulted in the active forcing of fluids. Previous to fluid administration (2 liters of 0.7 per cent. sodium chlorid solution subcutaneously) the hemoglobin value was 163 per cent. A few hours after the salt solution had been given the patient regained

3. Keith: Am. J. Physiol. **59**:452, 1922.
4. Underhill and Kapsinow: J. Biol. Chem., in press.

consciousness, became rational, and was capable of cooperation in taking of fluid. Blood concentration fell rapidly and the patient went on to recovery. The point to be emphasized here is that this patient on the eighth day after being burned still had a blood concentration equal to that in some of our own serious cases on the first day. The presumption is valid that if this patient's blood concentration would have returned to normal of itself it should have done so within a period of eight days, an interval during which none of our own patients maintained such a concentration. A comparison of the influence of water intake on blood concentration at an interval of one day and eight days (the case just discussed) is given in Chart 4.

From such data it would appear that water intake is responsible for the decrease in blood concentration observed in our cases, and it is quite safe to assert that without such water introduction blood concentration would not have taken the decided fall observed in every case. We believe, therefore, that the observations recorded justify the conclusion that water introduction in sufficient quantities to restore blood concentration to within normal limits is of paramount importance in the treatment of burned cases. As a result of this type of treatment, it may be stated that only two patients gave any evidences of symptoms characteristic of intoxication in burns. In these cases unconsciousness at first prevailed; this, however, disappeared after restoration of blood concentration. In all the other cases, the patients presented no untoward symptoms, such as delirium, unconsciousness, gastro-intestinal disturbance, hemoglobinuria, albuminuria, etc. Whether such facts are to be interpreted from the viewpoint that restoration of blood concentration prevented the development of conditions responsible for these symptoms, or that fluid introduction caused prompt elimination of toxic material so diluted as to be innocuous or both, remains a problem the solution of which can be determined only in the future. At any rate, from either viewpoint it would appear that fluid introduction is a rational method of treatment for extensive superficial burns.

CHANGES IN THE COMPOSITION OF THE BLOOD

During the first three or four days subsequent to the accident, analysis was made of blood taken from a vein. Particular attention was paid to the estimation of the nonprotein nitrogen fraction on the assumption that if absorption of nitrogenous toxic material occurred the possibility presented itself that an increase in nonprotein nitrogen might be anticipated. From Table 3 it may be seen that changes observable in the composition of the blood during burns vary at most only slightly from the normal limits. Where alterations are above those regarded as normal, the increases noted cannot be interpreted as evidences of absorption of unusual products, but in our opinion they are

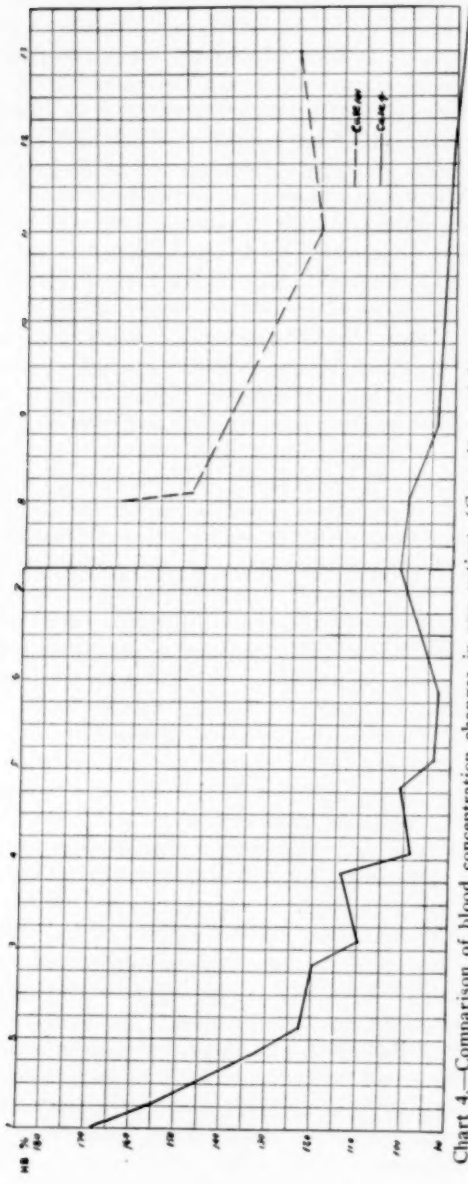


Chart 4.—Comparison of blood concentration changes in one patient (Case 4) receiving early adequate fluid intake and one patient (Case 101) receiving similar treatment eight days later.

rather to be regarded as the expression of the change that would be expected in blood highly concentrated. At any rate, until it can be demonstrated that the composition of the blood with respect to the fractions determined here are uninfluenced by concentration of blood to the degree noted in the cases under discussion, we prefer to accept the explanation that blood concentration is responsible for the changes in composition of the blood noted rather than to ascribe these changes to material absorbed from the burned areas.

In one respect the analyses of the blood appended are worthy of comment, namely, in the figures for chlorids. During health chlorids are remarkably constant, varying for whole blood from 0.45 to 0.50 per cent. calculated as sodium chlorid. It might, *a priori*, be expected that when rapid interchange of fluid occurs corresponding changes in salt balance would take place since it is to be assumed that when fluid leaves the tissues and blood in response to local inflammatory reactions the fluid poured on the surface is plasma or at least modified plasma. Certain it is that in war gas poisoning in the production of pulmonary edema the fluid entering the lungs has almost the same composition as that of the blood plasma. Moreover, under these circumstances which lead to highly concentrated blood the sodium chlorid of the blood decreases whereas the sodium chlorid of the lungs correspondingly increases. It is quite probable that applying similar reasoning to the process in burns whereby fluid is lost to the burned surface one should expect lowered chlorid content of the blood if the latter has reached a stage in fluid interchange in which normal water balance can no longer be maintained.

Although the figures are in no sense complete, the data on sodium chlorid content of the blood (Table 3) plainly indicate that this salt played a significant rôle in fluid interchange at least during the initial stage of the injury. In general, when blood was highly concentrated, the sodium chlorid content was distinctly low, and when the value for hemoglobin was not so greatly altered, the figures for sodium chlorid approach very closely those of the normal. Expressing it differently, almost without exception the sodium chlorid values were inversely as those for hemoglobin. On this basis the data for sodium chlorid divide the cases into two groups quite as sharply as the hemoglobin figures. It is, of course, quite probable that other constituents of the blood, especially the remaining inorganic components, play a distinct rôle in the water balance of the body. These possible changes were not investigated. It is quite apparent, however, that in the rapid interchange of fluid during the inflammatory stage of burns, sodium chlorid functions prominently. This observation tends to establish the hypothesis that in acute inflammatory processes the mechanism of fluid interchange in response to injury is of similar character whether the irritating agency is war gas or heat.

TABLE 3.—*Composition of the Blood*

Case	Date, 1921	Nonprotein Nitrogen, Mg. per 100 C.c.	Creatinin, Mg. per 100 C.c.	Creatin, Mg. per 100 C.c.	Sugar, Mg. per 100 C.c.	Urea, Mg. per 100 C.c.	Chlorids as NaCl in Percentage
1	Nov. 28	38.72	2.23	9.68	166.1	17.90	....
	29	34.96	3.26	8.34	177.9	.....	....
	30	36.08	2.14	17.65	172.4	16.14	0.37
2	Nov. 28	48.12	1.70	11.50	216.4	16.50	....
	29	63.60	3.26	9.37	194.2	27.02	0.31
	30	37.00	2.20	7.69	174.8	19.30	0.34
	Dec. 1	41.52	2.14	13.10	181.1	20.14	0.43
5	Nov. 28	38.52	1.50	.....	133.3	.....	....
	29	35.24	2.59	7.60	135.8	15.42	....
	30	27.92	1.87	14.29	146.1	15.86	0.37
6	Nov. 28	37.48	1.70	12.50	121.6	.....	....
	29	36.13	3.26	7.70	97.8	15.30	0.44
	30	33.72	2.14	14.63	181.1	19.68	....
7	Nov. 28	36.84	1.63	14.28	138.8	.....	0.47
	29	33.76	2.14	15.00	158.7	.....	0.41
	30	31.00	1.92	15.42	149.7	14.80	0.43
8	Nov. 28	42.64	1.59	9.20	133.6	9.42	0.44
	29	41.84	3.41	14.63	116.8	.....	....
	30	34.92	2.20	16.60	162.3	12.82	0.37
	Dec. 1	38.96	1.92	6.20	117.6	.....	....
9	Nov. 28	36.40	1.78	9.50	117.0	14.32	....
	29	33.48	3.00	7.70	99.4	8.72	....
	30	30.28	2.02	16.20	128.2	16.72	....
	Dec. 1	37.24	2.14	12.50	132.9	16.86	0.40
10	Nov. 28	55.32	1.74	14.29	199.2	22.98	0.33
	29	50.48	1.97	12.00	181.8	30.16	....
11	Nov. 28	34.72	1.87	9.23	133.3	.....	0.54
	29	31.64	3.00	7.50	122.5	.....	....
	30	31.08	1.97	13.95	181.1	13.06	0.39
	Dec. 1	36.72	2.82	12.00	139.6	16.32	0.36
12	Nov. 28	38.24	2.27	10.16	173.2	16.24	....
	29	39.04	2.59	8.70	120.4	16.26	....
	30	38.40	2.20	11.75	138.8	14.06	....
13	Nov. 29	48.80	2.88	10.55	196.3	.....	....
14	Nov. 28	31.36	1.66	15.00	131.2	18.18	0.37
	29	33.88	2.34	9.10	98.8	13.82	0.46
	30	27.44	1.87	15.80	150.6	15.00	0.45
15	Nov. 28	57.72	2.34	.....	187.9	.....	....
	29	67.44	3.57	9.68	146.1	22.98	0.38
	30	40 40	2.14	10.35	134.7	10.44	0.46
16	Nov. 28	25.84	1.83	8.82	156.2	.....	....
	29	34.36	3.26	7.23	99.8	14.55	....
	30	27.44	1.87	15.80	150.6	15.00	0.45
17	Nov. 28	30.52	1.87	10.35	110.6	12.02	0.48
18	Nov. 28	28.08	1.71	10.16	139.2	13.98	0.50
19	Nov. 28	28.16	1.63	9.09	107.8	13.58	....
	29	33.48	2.59	8.70	104.8	.....	0.47
	30	33.72	2.08	14.30	128.2	9.94	0.50
20	Nov. 28	29.60	1.59	10.00	159.7	13.02	....
	29	29.68	....	.....	.....	.....	....

Various estimations of the urinary constituents were also carried through. Owing to the fact that uncertainty exists as to accurate division into twenty-four-hour periods these data are omitted.

THE RELATION OF BLOOD CONCENTRATION TO BLOOD PRESSURE AND TEMPERATURE IN EXTENSIVE SUPERFICIAL BURNS

It is well recognized that in extensive superficial burns there may occur a notably low blood pressure which may be accompanied by other clinical signs of a shocklike condition or a state of impending shock. In the analysis of our cases it may be seen (Table 4) that systolic blood pressure in a number of instances is low, and that the pulse pressure is correspondingly diminished. This low pulse pressure coupled with the markedly accelerated heart beat, as indicated by the pulse record, may be taken as an indication of a failing circulation. Such conditions maintained for an extended period are most certain to lead to the clinical picture of shock. Although in the cases of burns under discussion an actual shocklike condition was lacking, it is quite evident that the circulatory disturbances manifested could readily be accepted as indicative of impending shock.

The reason for the rapid onset of circulatory failure in burn cases has not been definitely established. Without discussion of the various viewpoints that have been presented, one factor which may play a rôle is the existence of a highly concentrated blood. There can be no question that a noteworthy fall in pressure under various experimental conditions, as in so-called peptone shock or histamin shock, is accompanied by the rapid development of concentrated blood. The fall in pressure, per se, however, can hardly be accepted as the cause for the concentrated blood. On the other hand, a highly concentrated blood may so seriously interfere with the circulatory mechanism that a low blood pressure is the consequence. In gas poisoning, for instance, a shocklike condition may ultimately prevail which is assuredly the result of a failing circulation primarily induced by a blood highly concentrated; in other words, by a decreased blood volume. Applying these facts to our knowledge of the conditions attendant on injury through extensive superficial burns, and noting the similarity in the mechanism leading to circulatory failure, it is not illogical to assume that a highly concentrated blood may be, in large measure, a contributing factor in the development of a shocklike condition, or state bordering on shock. It may be noted, in general, that those cases with the highest initial blood concentration also presented the lowest pulse pressure. On the other hand, some cases showed a low pulse pressure with only a medium blood concentration, and some cases gave evidence of highly concentrated blood with normal pulse pressure. The resistance or sensitive-

TABLE 4.—*The Relationship of Blood Concentration to Blood Pressure and Temperature*

Case	Hemoglobin in Percentage	Fluid Intake, C.c.	Pulse	Temperature	Blood Pressure		
					Systolic	Diastolic	Pulse Pressure
1. Nov. 28	176, 197	3,750	105	103.5	120	65	55
29	174, 165	6,000	110	102-104	102	62	40
30	149, 158	5,800	100	102-104	...	..	..
Dec. 1	143, 135	5,980	100	102-104	124	74	50
2	122	5,340	100	102-104	...	..	..
3	131	5,000	100	102-103	112	68	44
4	135	5,000	100	102	...	..	..
5	127	5,000	95	101-102	128	70	58
2. Nov. 28	231, 214, 226	2,000	110	100-101	110	85	25
29	195, 214	4,150	100	98.6-102	122	84	38
30	156, 135	5,000	100	99.5-102	120	68	52
Dec. 1	126, 131	5,300	100	102-104	134	64	70
2	133 138	5,000	100	104	146	72	70
3	134	5,000	100	102-103	136	70	60
4	142	5,000	95	101-102	154	82	72
5. Nov. 28	167, 161, 155	3,500	95-120	98.4-102	114	75	39
29	150, 149	6,500	100-115	99-102	120	62	58
30	138, 120	7,470	100-110	101-102	130	68	62
Dec. 1	123, 123	6,400	100	101-102	148	72	76
2	112	7,300	100	100-102	142	78	64
3	123	7,000	100	100-101	144	84	60
4	...	5,000	95-110	100-101	...	..	..
5	123	5,000	100-110	99-101	154	82	72
6. Nov. 28	167, 160	1,200	100-105	101	136	86	50
29	153, 144	3,500	95-110	98.6-102	120	74	56
30	139, 131	6,570	90-100	99.5-101	132	66	66
Dec. 1	134, 135	7,400	85-100	99-103	128	76	52
2	123	6,000	80-100	100-103	124	72	52
3	115	6,200	75-100	100-101	138	86	52
4	...	4,500	65-85	99	...	..	..
5	114	4,500	65-75	99	122	70	52
7. Nov. 28	153, 150	3,400	80-110	101-104	118	78	40
29	167, 183	6,400	90-110	99.5-103	124	72	52
30	135, 135	5,500	80-90	99.5-103	128	68	60
Dec. 1	127, 133	4,950	85	99.5-103	122	76	46
2	119	6,375	80-95	101.5	124	70	54
3	133	6,800	70-90	100	130	78	52
4	...	6,000	80-95	99.5-105.5	...	..	..
5	133	6,000	80-90	100	128	74	54
8. Nov. 28	174, 200, 188	2,700	85-100	98-100	140	80	60
29	167, 183	5,820	85-105	99-100	136	80	56
30	143, 135	5,800	105	99-102	152	78	74
Dec. 1	127, 133	6,700	85-105	102-103	170	86	84
2	126, 150	6,600	105	102-104	168	74	94
3	139	7,000	100-105	102.5-103.5	156	62	94
4	146	6,000	80-90	101.5	...	..	..
5	130	5,000	80-100	100-101	162	72	90
9. Nov. 28	170, 174	2,300	90-110	98-101	102	70	32
29	165, 156	3,400	110-120	99.5-101.5	120	72	48
30	139	?	95-110	101-103	...	..	..
Dec. 1	135, 135	6,915	100-110	102-104	138	90	48
2	125	6,480	100-105	102	124	86	38
3	126	6,900	100-105	101.5-102.5	112	78	34
4	...	5,985	90-100	99.5-101	...	..	..
5	144	5,000	80-100	99.5-100.5	120	74	46
11. Nov. 28	165, 161	3,760	90-100	101-102	130	80	50
29	161, 161	6,580	90-100	101-103	132	80	52
30	152, 150	6,600	100-125	103-104	130	78	52
Dec. 1	133, 129	6,160	100-120	102-103	140	72	68
2	122	5,520	100	101-103	142	76	66
3	125	4,950	90-95	101-103	138	86	52
4	...	5,000	90-100	99-101	...	..	..
5	118	5,000	90-95	99-100	124	82	42
12. Nov. 28	167, 167, 169	2,300	60-105	99-100.5	100	68	32
29	172, 142	3,900	105-130	99-103	98	64	34
30	130, 129	4,700	110-130	102-103	88	58	30
Dec. 1	126, 125	6,340	105-110	102-103	82	48	34
2	143	4,450	90-110	102-103	104	64	40
3	119	4,100	105-110	102-103	102	52	50
4	...	4,000	90-105	100-102.5	...	..	..
5	...	4,000	90-105	100-102	110	54	56

TABLE 4.—*The Relationship of Blood Concentration to Blood Pressure and Temperature—(Continued)*

Case		Hemoglobin in Percentage	Fluid Intake, C.c.	Pulse	Temperature	Blood Pressure		
						Systolic	Diastolic	Pulse Pressure
13.	Nov. 28	200, 167, 183	3,400	100-130	99-100	90	75	15
	29	188, 176, 153	6,100	100-125	100-101	80	62	18
	30	153, 113, 128	7,200	110-120	100-101	110	78	32
	Dec. 1	123, 119	5,300	110-115	99.5-101	124	70	54
	2	109, 123	7,400	110-130	102-103	132	70	62
	5	120	6,000	95-120	102-103	138	84	54
	4	119	6,000	95-130	102-104	...	..	..
14.	Nov. 28	156, 130	3,900	100-120	100-103	94	66	28
	29	153, 128	4,300	110-120	100-102.5	102	64	38
	30	136, 135	4,900	100-125	99-103	98	70	28
	Dec. 1	119, 123	5,350	115-125	101-102	108	68	40
	2	120	5,250	105-120	99.5-102	106	64	42
	3	114	5,150	105-125	99.5-101.5	98	60	38
	4	...	5,000	95-105	98.6-99.6	...	..	..
	5	109	5,000	95-110	98-100	108	62	46
15.	Nov. 28	167, 139	900	110-130	98-102	104	84	20
	29	146, 133	3,700	95-125	101-102	96	78	18
	30	120, 130	4,550	95-120	101-102.5	96	68	28
	Dec. 1	95, 104	4,685	100-110	102-103	...	..	..
	2	103	5,800	100-105	102-103	124	64	60
	3	94	5,550	100-105	101-102	...	..	..
	4	...	5,000	100-110	101-102	...	..	..
	5	92	5,000	100	100-101	118	68	50
16.	Nov. 28	129, 120	3,300	100-105	98.6-100.5	92	65	27
	29	143, 136	5,050	85-105	99.5-100.5	104	63	61
	30	126, 131	5,060	95-110	99.5-101	94	68	26
	Dec. 1	122, 133	5,400	90-100	99-100	100	64	36
	2	130	5,050	95-120	98.6-99.5	104	64	40
	3	136	5,400	95-100	99.0-99.5	96	60	36
	4	133	5,000	80-130	98.6-99.7	...	..	..
	5	126	5,000	95-115	98.6-99.0	96	68	28
	6	125	5,000	85-100	98.6-99.0	...	..	..
17.	Nov. 28	150, 136	2,800	80-90	99.5-100.5	154	108	46
18.	Nov. 28	134, 114	3,700	90-110	99-100	114	75	39
19.	Nov. 28	129, 129	4,200	80-95	99-100.5	110	85	25
	29	127, 138	5,250	90-110	99-102	118	80	38
	30	139, 142	5,250	100-118	100-101	108	76	32
	Dec. 1	129, 130	5,000	105-110	100-101	118	74	44
	2	120	5,200	95-120	99-100.5	112	70	50
	3	150	5,400	95-110	99.5-100.5	108	74	34
	4	...	5,000	85-100	97.5-99	...	..	..
	5	110	5,000	80-90	97.5-99.5	110	68	32
	6	128	5,000	80-85	98-98.6	...	..	..
20.	Nov. 28	135, 120	3,800	105-120	100.5	120	82	38
	29	122, 125	5,700	100-110	99-101	110	64	46
	30	128, 113	5,000	70-110	101-102.5	118	60	58
	Dec. 1	117, 115	5,000	90-110	99.5-100	...	..	..

ness of persons to impending shock is well recognized, and dogmatism relative to the degree of blood concentration necessary to produce a failing circulation in any given case is outside the limits of the present discussion.

If blood concentration is an important incident in the development of shock in burn cases, it would be logical to assume that treatment designed to restore blood concentration to a normal level should also be beneficial in the restoration to normal of the pulse pressure. In Table 4 it is shown that fluid introduction not only caused the blood to return to a more normal level, but that the blood pressure also improved

to a notable degree. From these data, then, it would appear suggestive at least that fluid intake should improve the circulation by increasing blood pressure. From the observations available, it is indicated that blood concentration may play a distinct rôle in the production of a low blood pressure characteristic of certain burn cases.

The relationship of temperature to blood concentration is close. In war gas poisoning cases temperature changes take place in one of two directions as a result of the degree of blood concentration. With a moderate blood concentration, and with the circulation maintained close to normal limits, the temperature rises above the normal. If blood concentration proceeds to a point at which approximate normal efficiency of the circulation fails, the temperature falls rapidly to a point far below the normal, culminating in death. From experience with gas poisoning cases, the conclusion was drawn "that the temperature is directly related to the efficiency of the circulation, and this, in turn, is determined, in part at least, by the concentration of the blood and the pulse rate." In the observations here discussed the data relative to temperature changes are not so clear cut as obtain with blood pressure. The association of blood concentration with the initial rise in temperature is, however, quite obvious, and it is possible that this increase in temperature may be taken as an expression of the effect of a highly concentrated blood. The later much higher augmented temperature is undoubtedly to be interpreted as a sequence of infection of the injured areas.

SUMMARY

In extensive superficial burns the blood becomes highly concentrated. This increased concentration of the blood is regarded as an important factor in the development of many of the clinical signs and symptoms characteristic of burns. The recognition that in extensive burns the blood becomes highly concentrated leads to a rational method of treatment to obviate the untoward symptoms.

Restoration of normal blood concentration by adequate forcing of fluid is accompanied by marked evidences of improvement and the development of the usual sequels (delirium, unconsciousness, gastrointestinal disturbances, albuminuria, hemoglobinuria) of extensive burns is checked. The vast majority of badly burned patients ultimately recover.

Decrease of blood concentration to a point near the normal limits is, therefore, of prime importance in the systemic treatment of burn cases. The determination of the degree of blood concentration may be regarded as an index of the patient's general condition, and will also indicate the extent to which fluid should be forced. The relationship of blood concentration to fluid interchange in inflammatory reactions, with special reference to blood composition and circulatory failure in burns, is discussed by illustrative cases.

REPORT OF CASES [5]

CASE 1.—A man, aged 18, a student, who had had measles, mumps, scarlet fever and typhoid, and whose family history was irrelevant, had sustained first and second degree burns of the entire face, hands and ears. Heart and lungs negative.

Treatment [6] consisted of paraffin sprays applied to the burned areas, followed later by skin grafting. No complications arose during convalescence. Recovery was complete.

CASE 2.—A man, aged 22, had had typhoid fever. His mother had been treated for tuberculosis. His father died in a fire. The patient had sustained first and second degree burns of the face and hands. The heart and lungs were negative.

Treatment consisted in immersing the hands in boric acid solution. The face was sprayed with paraffin. Skin grafts were applied to the ears and hands. No complications ensued. The patient recovered completely.

CASE 3.—A woman, aged 25, a telephone operator, had had influenza three years ago. A slight cough has persisted since. Otherwise her history is negative. The family history is irrelevant. Second degree burns involved the face, eyelids, nose, cheeks, chin, ears, arms, wrist and hands, with first and second degree burns of the back, buttocks and the backs of the thighs. The pulse was rapid and of poor quality. The heart and lungs were not examined because of the poor condition of the patient.

Treatment consisted of continuous tub baths. The pulse rose to 160. It was irregular and of poor quality. The woman died twenty hours after admission.

CASE 4.—A girl, aged 5, whose personal and family histories were not complete, sustained a second degree burn of the entire face and of both arms to the elbow, and first degree burns of both legs. The heart and lungs were essentially negative, except for a rapid pulse on admission.

Treatment consisted of the use of petrolatum and boric acid ointment dressings. Complications were: purulent otitis media and conjunctivitis with hypopyon. Seventeen days after the accident pneumonia developed. Oxygen was administered through a nasal catheter. The patient died twenty-four hours after the development of the pneumonia, on the eighteenth day after the accident.

CASE 5.—Man, aged 21, a truck driver, with irrelevant personal and family histories, sustained first and second degree burns of the face, ears and hands. The heart and lungs are negative.

All burned areas were cleaned with boric acid compresses. Later skin grafts were applied. Recovery was complete.

CASE 6.—A man, aged 21, a student, who had had mumps, measles and whooping cough, with irrelevant family history, sustained second degree burns of the face and hands. The heart and lungs were negative.

Boric acid ointment was applied to the face. The hands were immersed in boric acid solution. Recovery was complete.

CASE 7.—A man, aged 22, a plumber, who had had the usual childhood diseases, and whose family history was irrelevant, presented chiefly first degree burns of the face, neck and hands. The lungs were negative. The heart, except for an occasional extra systole, was negative.

Treatment consisted of the application of continuous wet dressings of boric acid solution, and skin grafts to the ears. Recovery was complete.

---

5. The data herein recorded are added for the purpose of showing the extent of the burns. No attempt has been made to give a detailed account of the clinical signs and symptoms.

6. In all cases systemic treatment consisted in the forcing of fluid.

CASE 8.—A man, aged 18, a student, who had had the usual diseases of childhood, sustained second degree burns of the face, neck and hands. His heart and lungs were negative.

Treatment consisted of constant wet dressings of boric acid solution applied to all burned areas, and the application of skin grafts to the ears and hands. Recovery was complete.

CASE 9.—A man, aged 21, a student, had had pneumonia and rheumatic pains in the shoulder and knees. His family history was essentially negative. He sustained second degree burns of the face, neck and ears and first degree burns of the hands and legs. His heart and lungs were negative.

Constant wet dressings of boric acid solution were applied to the burned areas. Skin grafts were applied to both ears. Recovery was complete.

CASE 10.—Middle aged man with meager history. First and second degree burns on hands, face, feet and legs.

CASE 11.—A man, aged 18, a student, who had had the usual diseases of childhood, and whose family history was essentially negative, sustained first and second degree burns of the face and hands. His heart and lungs were negative.

A paraffin film was applied to the face. The hands were immersed in boric acid solution. Skin grafts were applied to the hands and ears. Recovery was complete.

CASE 12.—A woman, aged 47, a housewife, with essentially negative history, sustained first and second degree burns of the face and hands. The heart and lungs were negative.

Picric acid solution was applied to the burned areas. Skin grafts were applied to the hands and ears. Recovery was complete.

CASE 13.—A woman, aged 37, a housewife, was admitted in a very serious condition entailed by severe second degree burns of the face and hands, and first degree burns of the chest, back and legs. The patient was very obese. The heart and lungs were not examined.

Paraffin sprays were applied locally. Pneumonia developed seven days later and the woman died.

CASE 14.—A woman, aged 24, a housewife, with irrelevant history, sustained first and second degree burns of the face, neck, shoulders, chest and hands.

Paraffin was sprayed locally. Recovery was complete.

CASE 15.—A woman, aged 25, a housewife, whose husband was also burned, sustained second and third degree burns of the hands, face and legs. Her heart and lungs were negative.

Picric acid powder was applied to the burned areas. The patient was removed by her private physician to her home for treatment. Recovery was not reported.

CASE 16.—A woman, aged 27, a nurse, who had had scarlet fever, sustained first and second degree burns of the hands and face. Her heart and lungs were negative.

Paraffin was applied locally. Recovery was complete.

CASE 17.—A woman, aged 63, a housewife, had been treated for high blood pressure. She had had a "shock." Second degree burns of both hands were incurred as well as first degree burns of the nose. A loud systolic aortic murmur was heard. The pulse beat was irregular. Blood pressure was 200/130. The lungs were negative.

Paraffin sprays and boric acid ointment were applied locally. The patient left against advice. Recovery was not reported.

CASE 18.—A woman, aged 23, a clerk, had had measles and scarlet fever during childhood. She sustained first and second degree burns of the face and hands. The heart and lungs were negative.

Treatment consisted of paraffin sprays and boric acid ointment applied locally. She left against advice. Recovery was not reported.

CASE 19.—A woman, aged 28, a housewife, who had had the usual diseases of childhood, sustained first degree burns of the face, and first and second degree burns of the hands. Her father was burned at the same time.

Treatment consisted of local paraffin sprays. Recovery was complete.

CASE 20.—A woman, aged 31, a housewife, who had had the usual diseases of childhood, sustained first and second degree burns of the arms and hands, and first degree burns of the nose and legs. Her heart and lungs were negative.

Treatment consisted of local paraffin sprays. She was discharged to her family physician for further treatment. Recovery was not reported.

CASE 21.—A man, aged 18, a printer, who had had the usual diseases of childhood, and whose father died from tuberculosis and the mother from pneumonia, sustained first degree burns of the right cheek. His heart and lungs were negative.

Treatment consisted of the use of boric acid ointment locally. Recovery was complete.

OBSERVATIONS ON ONE HUNDRED AND NINETY-TWO CONSECUTIVE DAYS OF THE BASAL METABOLISM, FOOD INTAKE, PULSE RATE, AND BODY WEIGHT IN A PATIENT WITH EXOPHTHALMIC GOITER*

CYRUS C. STURGIS, M.D.

BOSTON

Careful studies during recent years have demonstrated, beyond question, that an elevation of the basal metabolism is a constant finding in the syndrome of exophthalmic goiter. Many careful observations have definitely established this fact and render additional and similar investigation in this direction superfluous. It seems probable, however, that further useful knowledge may be gained by the careful and intensive study of the daily metabolism of persons with exophthalmic goiter over a long period of time. By so doing our information concerning the relationship between the heightened metabolism and this disease may become more accurate and thereby extend the usefulness of basal metabolism determinations in clinical medicine. The present series of observations of the metabolism of a patient with exophthalmic goiter continued over an interval of 202 days, and the determinations were made for the purpose of securing data bearing on the following questions:

1. The range of variation in the basal metabolism in exophthalmic goiter on consecutive days.

2. The relationship between the basal metabolism and the resting pulse, food intake and body weight.

3. The effect of various types of treatment on the daily basal metabolism.

Incidentally, an opportunity was afforded to note the effect of an acute infection on the course of the disease, and to ascertain the influence of the menstrual cycle on the basal metabolism.

REPORT OF A CASE

History.—The patient was an Irish woman, aged 32 years, who entered the hospital complaining of "nervousness." She had always been strong and healthy, with the exception of rather severe attacks of tonsillitis, which had occurred almost every year. The last attack had occurred two years before. She had been married for thirteen years, and her family consisted of two healthy girls, 12 and 8 years of age. She had always worked hard, caring for her own household entirely alone, and doing laundry work for private families five days out of the week. Her husband had been unable to obtain work for some

* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

time, and this had added to the strain of extra labor which she had been obliged to perform. She had worried considerably about "making both ends meet."

The onset of the present illness occurred about six months before admission, when she noticed that she became unusually tired and nervous at the end of a day's work. She was inclined to be "high strung" and developed emotional instability in the form of frequent attacks of weeping. At this time, she suffered from palpitation and moderate dyspnea on exertion. Her appetite became unusually hearty, yet her weight steadily decreased from 155 pounds (70.3 kg.) to 125 pounds (56.7 kg.) in six months. She observed a continuous feeling of warmth and an abnormal tendency to perspire. On account of this feeling of warmth, she used few bed clothes and did not dress heavily even in the coldest weather. Her husband had noticed for several months previous to admission that her face had become darker, and that there was a slight puffiness under the eyes. Her condition gradually became worse, although she had continued to do her own household duties as well as outside laundry work until the day of admission.

Physical Examination.—The patient was well developed and nourished. She had the characteristic demeanor and quick movements so often observed in a

TABLE 1.—*Order of Observations*

	Date	Day of Observation
Admitted to hospital	March 1	1st
Acute tonsillitis	From March 13 to March 18	12th to 17th
Forced feeding begun and continued throughout patient's stay in the hospital	March 29	28th
Roentgen-ray treatments:		
1st	April 15	45th
2d	May 2	62d
3d	May 23	83d
4th	June 13	104th
Ligation of left superior thyroid artery	July 27	142d
Ligation of right superior thyroid artery	July 31	146th
Thyroidectomy attempted; unfavorable reaction toward anesthetization	August 16	162d
Thyroidectomy under local anesthesia	August 22	168th
Discharged from hospital	September 19	202d

patient with exophthalmic goiter. Her face had a slightly dark brown tint. There was no outspoken exophthalmos, although the eyes were somewhat prominent. There was a suggestive lid lag. The heart was not enlarged. The pulse was regular, of the collapsing type, and the rate was rapid. There was moderate enlargement of the thyroid gland, which included both lobes and the isthmus. There was a systolic thrill over both lobes, and a systolic and diastolic bruit. The skin was warm and moist. There was marked characteristic tremor of the extended fingers.

Urine Examination.—Urinalysis revealed: albumin, 0; sugar, 0; the sediment showed rare white blood cells, no red blood cells or casts.

Roentgen-Ray Examination.—The chest was symmetrical with a normal diaphragm. The heart was somewhat enlarged, and the tracheal shadow was somewhat constricted and displaced toward the left side. The lung fields were essentially clear.

In the electrocardiogram, the curves were normal, with the exception of a slight prolongation of the P-R conduction time.

Course in Hospital.—The patient remained at complete rest in bed in the hospital, with the exception of walking to the toilet once or twice daily. She was permitted to eat all she desired, and a particular attempt was made to furnish her with the articles of diet which appealed to her taste. On March 12, ten days after admission, the patient developed an acute tonsillitis with fever,

which persisted for six days, and at intervals reached 103 F. On March 20, twenty-seven days after admission, a special effort was begun to encourage the patient to eat more food. From that date until April 15, a period of nineteen days, no other treatment than a high caloric diet and rest in bed was given. On April 15, after the patient had been in the hospital for forty-five days, the first roentgen-ray treatment over the thyroid gland was given, and three additional treatments at intervals of approximately three weeks followed. The patient was then observed for a period of forty-four days after the last treatment to determine the result of this therapy. As no change was apparent in the basal metabolism at the end of that time, it was decided that surgery was advisable. Accordingly, on July 27, the left superior thyroid was ligated under procain. On July 31, a similar procedure was performed on the right superior thyroid artery. On August 16, sixteen days after the last ligation, an attempt was made to perform a thyroidectomy; but the patient developed such an alarming reaction, following the administration of the anesthetic, that the operation was abandoned for that day. Six days later, on August 22, the right lobe and about three-fourths of the isthmus were removed under local anesthesia. For several days following the operation the patient was in an extremely precarious condition. Her condition greatly improved, and she left the hospital on September 19, on the two hundred and second day of observation. Her condition subjectively and objectively was improved although the metabolic rate remained elevated, averaging about 25 per cent. above normal. Arrangements were made so that she could rest at home and return to the hospital once a week for observation and advice concerning her future care. The chronological sequence of events which occurred during the period of observation of this patient is given in summary in Table 1.

METHODS OF STUDY

The patient's metabolism was determined each morning at approximately the same hour (8:30 to 9 a. m.) after a complete fast of from twelve to fourteen hours. The heat production was calculated by indirect calorimetry, and rigid attention to all details was observed in order to make the results as accurate as possible. The expired air was collected by means of a half mask and a modified Tissot spirometer, equipped with suitable valves, for a minimum of two nine minute periods.[1] A different spirometer, mask and valves were used for each period, and duplicate check analyses on the portable

1. The patient was under continuous observation in the hospital from March 1, 1922, to Sept. 19, 1922, an interval of two hundred and two days, with the exception of six days from June 16 to June 21, inclusive. She was permitted to return home at this time, as she was worried about the care of her children, and it was thought that a short visit to her home would permit her to adjust her household affairs and relieve her mind of this source of anxiety. She remained in bed at home throughout her visit of six days. The patient's metabolism was noted for two full nine-minute periods on each day that she was in the hospital, with the following exceptions: On July 30 and September 4, one period, and on September 19, both periods were lost as a result of technical errors. On August 16, a determination could not be made as the patient was completely anesthetized on that day. On the second and third days following the operation the patient's condition did not permit the metabolism to be determined. On August 22, about two hours after the thyroidectomy, only one six-minute period was obtained, and on August 23, the first postoperative day, the results were calculated from one seven-minute period. Therefore, while the patient remained under observation for two hundred and two days, she was in the hospital only one hundred and ninety-six days, the basal metabolism was determined on one hundred and ninety-two, and two satisfactory nine-minute periods were obtained on one hundred and eighty-eight.

Haldane gas-analysis machine were required on each sample of expired air. Outdoor air analyses were performed, at intervals, on each gas analysis apparatus. By such an arrangement, therefore, the metabolism in each period was estimated by a totally different set of apparatus, which obviated the occurrence of an undiscovered error in technic. The adherence to such a procedure, which is somewhat more elaborate than is usually used in clinical metabolism studies, was deemed essential in this work in order to appraise properly the minor changes in metabolism on consecutive days. The basal metabolism, when calculated from single periods, though of value when considered with the clinical data concerning the patient, cannot be regarded as highly accurate.

One hundred and ninety-two basal metabolism determinations were made on this patient. It seems a fair criterion in clinical medicine that the final metabolism result be expressed as the average of two periods which check within 5 per cent.[2] of each other. The following is a summary of the 188 metabolism estimations made on this patient, with a statement concerning the accuracy of the result as indicated by the approximation of the two periods. On thirty-eight days, the two periods agreed absolutely; on forty-seven days, they were within 1 per cent. of each other; on thirty-five days, they were within 2 per cent.; on thirty-two days, within 3 per cent.; on eighteen days, within 4 per cent., and on nine days, within 5 per cent. A consideration of the foregoing figures shows that in 81 per cent. of the determinations the two periods of each day's determinations were within 3 per cent. of each other, while in 94.5 they were within 5 per cent. of each other. There were ten determinations wherein the periods varied more than 5 per cent., the differences being as follows: three of 6 per cent.; three of 7 per cent.; two of 8 per cent.; one of 10 per cent., and one of 11 per cent. These differences all occurred either during the first few weeks after the patient's admission, or in the few weeks following the thyroid artery ligations and the lobectomy, both intervals during which the patient's condition was very unstable. From March 20 until August 11, an interval of 134 days, the two periods on each day agreed within 5 per cent.

DAILY VARIATION IN BASAL METABOLISM

There is no data in the literature bearing on the daily variation in the basal metabolism on consecutive days in patients with exophthalmic goiter. Benedict [3] has discussed this variation in normal men, and in a series of thirty-five men he found that in periods from five to fifty-three days, in experiments which extended over an interval varying from five days to four years and five months, the minimum and maximum variations were 3.5 per cent. and 31.3 per cent., respectively. Benedict and Cathcart,[4] in the course of studies wherein the daily metabolism of a person was determined almost daily from Dec. 7, 1911, to Feb. 29, 1912, reported that the oxygen consumption varied from a

2. All results of the basal metabolism determinations throughout this paper are expressed in per cent. of the average normal according to the standards of DuBois. Hereafter the percentage increase over the average normal is indicated by the figure with a plus sign preceding it.

3. Benedict, Francis G.: Factors Affecting Basal Metabolism, J. Biol. Chem. **20**:263, 1915.

4. Benedict, Francis G., and Cathcart, Edward P.: Muscular Work. A Metabolic Study with Special Reference to the Efficiency of the Human Body as a Machine, Washington, D. C., 1913 Carnegie Institution of Washington.

minimum of 225 c.c. to a maximum of 262 c.c., although the environment and diet of the person remained constant, except on certain days when conditions were admittedly abnormal, and on these the metabolism results were therefore excluded. Benedict concludes that the basal metabolism of a person is a function, first, of the total mass of active protoplasmic tissue, and second, of the stimulus to cellular activity existing at the time the measurement of the metabolism determination is made. The latter, he feels, accounts for the variations in the metabolism of normal persons which occurs from day to day.

In order to obtain an accurate estimate of the variation in the basal metabolism of the patient herein reported, it was necessary to exclude certain days when such abnormal factors as fever and operative procedures were adequate to account for marked changes in the basal metabolism. With the exception of a febrile period of five days, which was associated with an acute tonsillitis, and of several days immediately following the thyroid artery ligations and thyroidectomy, when there was slight fever, the patient's temperature did not exceed 99 F. by mouth. The body temperature was carefully determined after the patient came to the laboratory, once just before the first metabolism period and again between the first and second periods. With the elimination of the periods, when obviously abnormal conditions prevailed, there remained the observations on 142 days, on which conclusions may be based.

The greatest fluctuations in the metabolic rate occurred during the patient's first eleven days in the hospital. During this time (Chart 1) the greatest change from one day to the next amounted to 33 per cent., this being the difference between the determinations on the first and second days. This merely emphasized what is already well known but not fully appreciated by many clinicians, that, owing to apprehension, the first metabolism determination on any patient is likely to be higher than subsequent ones. It is interesting to note, however, that in the observations between the tenth and eleventh days after the patient's apprehension had been completely eliminated, there was a change as great as 23 per cent. This clearly illustrates that not only the initial, but some of the early subsequent, metabolism tests may show a change of considerable magnitude, which may easily lead to an incorrect judgment as to the future care of the patient. This is strikingly apparent on considering Chart 1. If only two isolated observations had been made on this patient, one on the first day and one on the eleventh day, the conclusion would have been that the metabolism was falling rapidly; had the two observations been made on the second and tenth days, the conclusion would have been that the metabolism was remaining stationary; had they been made on the eighth and tenth days, the conclusion would have been that the metabolism was rising. Two

observations, therefore, do not indicate in every patient whether the course of the disease is upward, downward or stationary, but more tests must be made which will more nearly form a curve on which to base judgment. A survey of the patient's daily metabolic rate from March 19 to July 26, just before the operative procedures were insti-

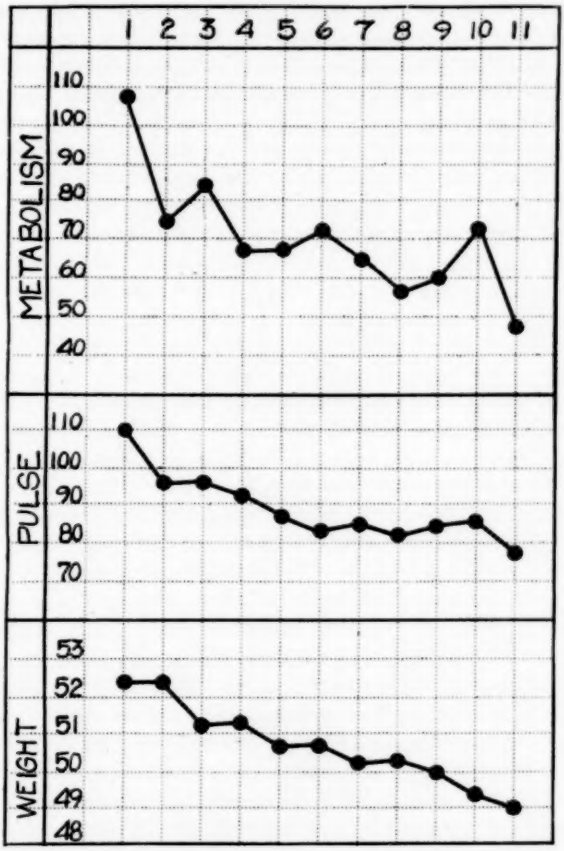


Chart 1.—The basal metabolism in per cent. of the average normal person, resting pulse rate per minute and body weight in kilograms for the first eleven days in the hospital. Note the difference (34 per cent.) between the determinations on the first and second days, and also the difference (23 per cent.) between the determinations on the tenth and eleventh days.

tuted, indicates that the patient's condition had become stable. During this interval of 123 days, the level of the basal metabolism remained remarkably constant. In this series of 123 estimations on consecutive

days, the greatest daily difference was 14 per cent. In 80.5 per cent. of the determinations, the variations from one day to the next were within 5 per cent. of each other, which is considered not above the limit of error; in 96 per cent. the variation was within 8 per cent.; in only three instances was the daily variation over 10 per cent.; these differences were 13, 14 and 11 per cent. The greatest variations often followed a period when the patient was nervous or upset over home conditions, and in a number of instances they followed a more or less sleepless night. It is to be expected that changes in the basal metabolism would occur in a patient with exophthalmic goiter under the influence of nervousness, worry, apprehension or fear; and it seems remarkable that even greater fluctuations did not result from such factors in a patient with a disease which is characterized by marked emotional instability. In rare instances, however, there were changes in the metabolism which could not be accounted for by excitement or other known factors. It is impossible to state whether these fluctuations resulted from variations in the stimulus, which is the cause of the accelerated metabolism in exophthalmic goiter, or whether they were due to slight muscular movements which escaped notice despite the closest observation. These observations emphasize the importance in clinical medicine of a conservative attitude toward the interpretation of single metabolism determinations. A few isolated tests, particularly during the first week or two of the observation period, might easily lead one to an erroneous conclusion concerning the course of the disease. After the patient's condition has become more or less stable, the fluctuations in the metabolism are much less, but even then they may in rare instances amount to as much as 14 per cent. from one day to the next.

THE RESTING PULSE RATE

A study of the correlation between the resting pulse rate and the basal metabolism in this patient revealed little in addition to what has already been observed. The resting pulse was determined according to the method previously described.[5] Immediately after the patient was brought to the laboratory, the radial pulse rate was counted for a full minute every third minute while the patient was resting quietly in bed. After the pulse rate had become constant, which was usually in one-half hour, the expired air was collected for two nine-minute periods. During these two periods the pulse rate was counted every third minute, and the average of these counts has been taken as the resting pulse rate. It is of interest to note that this patient fell into the rather small group of persons who have an increased metabolism and a relatively

5. Sturgis, Cyrus C., and Tompkins, Edna H.: A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, Arch. Int. Med. **26**:467 (Oct.) 1920.

slow pulse rate. The initial metabolism observation was + 108, while her pulse rate at this time was 110 per minute, which is somewhat lower than is ordinarily encountered in association with such high metabolism. Thereafter, during a greater part of the patient's stay in the hospital, the pulse rate was usually between 75 and 85 per minute. Once the ratio between the basal metabolism and the pulse rate had been established, the latter indicated accurately the changes in the metabolism with few exceptions. Read [6] has studied the correlation between the basal metabolic rate and pulse and pulse pressure and has observed that a patient with an increased metabolism and a relatively slow pulse is likely to have a high pulse pressure. He is of the opinion, therefore, that a combination of the pulse rate and pulse pressure is a better index of the response of the circulatory system than either one when considered alone. It is of interest in this patient that in association with the relatively slow pulse, the pulse pressure was always rather large, fluctuating between 70 and 90 mm. of mercury, which is in accord with Read's observations.

RELATIONSHIP BETWEEN THE FOOD CONSUMPTION, ENERGY EXPENDITURE, AND BODY WEIGHT

Friedrich Müller [7] first called attention to the loss of body weight and nitrogen in patients with exophthalmic goiter, despite the large amount of food consumed, and it was he who first emphasized that this was an indication of an accelerated metabolism. It is now well established that the dietary requirements are increased in patients with this disease on account of their increased heat production. The combination, therefore, of a large food intake and a loss or failure to gain in body weight, when encountered in the clinical history of a patient, should suggest the possibility that the patient's metabolism is increased. The only other common clinical entity which presents these circumstances is diabetes mellitus. Patients with an increased metabolism do not always lose weight. It may occur that the food consumption is so large that it compensates adequately for the dissipated energy and at the same time provides sufficient calories to permit the deposition of fat and protein in the form of body tissue, with a resultant substantial increase in body weight. In order to obtain more accurate data concerning the correlation between the food consumption, body weight and metabolism in patients with hyperthyroidism, a survey was made from the records of this hospital of fifty patients with hyperthyroidism. The average basal metabolism of this group was + 44

6. Read, J. Marion: Correlation of Basal Metabolic Rate with Pulse Rate and Pulse Pressure, J. A. M. A. **78**:1889 (June 17) 1922.

7. Müller, Friedrich: Für Kennt der Basedow's Krankheit, Deutsch. Arch. f. klin. Med. **51**:335, 1893.

per cent.; the lowest metabolism encountered in the series was + 18 per cent., while the highest was + 86 per cent. Thirty-eight or 76 per cent. of these patients gave a history of loss of weight, averaging 26 pounds (11.79 kg.), over an average length of time of eleven months. In 68 per cent. of the cases, there was a statement in the history that the loss of weight had occurred even though the appetite had been good or abnormally hearty. The combination of an elevated metabolism and a small food intake results inevitably in a marked loss of weight due to the consumption of the person's own tissue in order to supply the caloric requirements. One patient in this group had a poor appetite for eighteen months, and throughout this interval his metabolism remained moderately increased. There was a resultant decrease in body weight from 220 pounds (99.79 kg.) to 115 pounds (52.16 kg.). The loss, gain or stationary level of the body weight depends on the relationship between two factors: the energy provided in the form of food, and the total amount of energy expended, which is dependent chiefly on the level of the basal metabolism and the amount of muscular activity. One patient of this group gained 50 pounds (22.68 kg.) in three months, though he was not resting in bed and regardless of the elevation in his basal metabolism, which was always over + 50 per cent. His appetite during this period was insatiable.

Hirschlaff [8] has reported the most intensive, careful and complete metabolism studies of a patient with exophthalmic goiter. The patient was a girl, aged 21 years, who had the classical symptoms and signs of the disease. For forty-six days the average food consumption in calories was 5,300. It was calculated that food amounting to 360 calories were lost daily in the feces. During the time the patient's weight increased from 41.7 to 53.5 kilograms, a gain of 11.8 kg. This observer calculated that 5.6 kg. of this represented "flesh" while 6.2 kg. was stored as fat. Boothby [9] studied the food intake and basal metabolism in two patients with hyperthyroidism and decided that the caloric requirements in these patients was about 75 per cent. greater than the requirements as calculated from the basal metabolism.

The studies on the patient herein reported are summarized in Table 2. The average daily food intake for each week is shown in grams of protein, fat, carbohydrate and total calories, while the energy expenditure is represented by the column of figures showing the average daily basal metabolism for twenty-four hours. In addition, a column has been included which represents the average basal metabolism per twenty-

8. Hirschlaff, W.: Zur Pathologie und Klinik des Morbus Basedowii, Ztschr. f. klin. Med. **36**:200, 1899.

9. Boothby, Walter M., and Sandiford, Irene: A Preliminary Note on the Food Requirement in Hyperthyroidism, Med. Clin. of N. A. **5**:425 (Sept.) 1921.

tour hours, to which has been added 10 per cent. for the specific dynamic action of food, and 15 per cent. for additional movements while the patient is in bed. If the assumption as to the amount of calories consumed in the specific dynamic action of food and the movements in bed are correct, the figures in this column should indicate, theoretically, the approximate amount of energy expended by the patient each twenty-four hours. The last column shows the average weight per week in kilograms.

A consideration of Table 2 shows that the daily average food intake for a period of twenty-eight weeks was 3,953 calories per twenty-four hours, while the average daily energy expenditure, according to the method of computation already stated, was 2,349 calories. The differ-

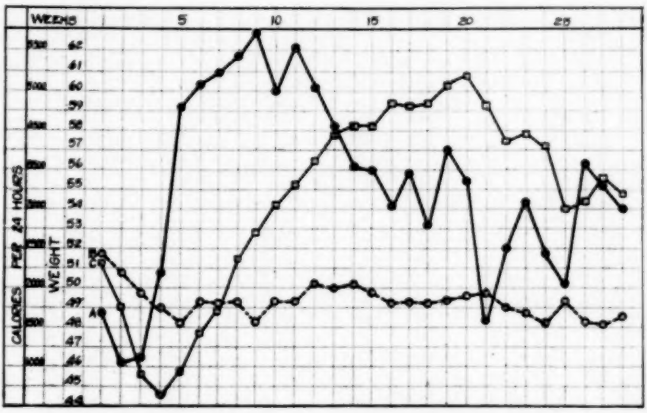


Chart 2.—Relationship between the average twenty-four hour caloric intake and expenditure and body weight per week for twenty-eight weeks. *A*, number of calories in the form of food consumed by the patient; *B*, energy expenditure per twenty-four hours calculated from the basal metabolism, to which has been added 10 per cent. of the total caloric intake for the specific dynamic action of food, and 15 per cent. for additional movements while the patient was resting in bed; *C*, body weight in kilograms. The average weekly energy expenditure remained fairly constant throughout the entire observation period, while the body weight, which varied widely, was directly proportional to the amount of food consumed.

ence between the energy intake and expenditure is, therefore, 1,604 calories, which must be accounted for by: (*a*) food which is not absorbed but is lost in the feces, (*b*) food which is ingested and absorbed but not burned and, therefore, stored as body fat and protein (c) additional movements which are eliminated during the basal period but are present more or less constantly during the day. Any additional

energy expenditure held to be accounted for under this head, then, would indicate that the original theoretical allowance of 15 per cent. for movements while in bed was inadequate.

A consideration of the investigations relating to the utilization of food in patients with exophthalmic goiter indicates that as much food is absorbed as in a normal person. The average of the various food constituents found in the stool, as reported by F. Müller and Hirschlaff,[10] is as follows: carbohydrate 6.2 per cent., fat 10.9 per cent. and nitrogen 8.1 per cent. Applying these averages to the protein, fat and

TABLE 2.—*The Daily Average Food Intake, Basal Metabolism, Estimated Total Energy Expenditure and Body Weight per Week for Twenty-Eight Weeks*

Weeks	Date	Food Intake				Basal Metabolism per 24 Hours	Basal Metabolism per 24 Hours + 25 per Cent.*	Body Weight
		Protein	Fat	Carbohydrate	Calories			
1	March 8	76	127	233	2,448	2,311	2,889	51.4
2	15	54	89	132	1,560	3,235	2,723	49.0
3	22	52	89	165	1,717	1,972	2,452	45.6
4	29	87	143	263	2,765	1,776	2,250	44.8
5	April 5	101	350	305	4,920	1,774	2,775	45.7
6	12	106	363	336	5,188	1,851	2,331	47.6
7	19	108	370	295	5,093	1,838	2,297	49.0
8	26	106	379	397	5,587	1,885	2,357	51.5
9	May 3	120	397	422	5,914	1,960	2,110	53.5
10	10	104	353	412	5,389	1,911	2,389	54.9
11	17	106	398	377	5,678	1,897	2,390	56.2
12	24	93	352	406	5,320	2,064	2,580	56.5
13	31	90	326	331	4,758	2,029	2,554	58.0
14	June 7	75	271	326	4,164	2,046	2,558	58.1
15	14	70	279	303	4,124	1,946	2,415	58.1
16	27	70	223	256	3,411	1,865	2,382	59.5
17	July 4	77	255	324	4,016	1,889	2,374	59.4
18	11	80	260	299	3,972	1,862	2,328	59.6
19	18	86	301	325	4,484	1,874	2,343	60.3
20	25	80	244	322	3,917	1,922	2,402	60.9
21	Aug. 1	41	124	186	2,084	1,947	2,438	59.5
22	8	43	200	260	3,102	1,796	2,249	57.5
23	15	72	226	321	3,713	1,779	2,227	57.9
24	22	60	196	234	3,000	1,676	2,094	57.2
25	29	41	160	230	2,599	1,805	2,344	54.0
26	Sept. 5	89	278	323	4,275	1,637	2,046	54.3
27	12	76	254	288	3,855	1,633	2,028	55.1
28	19	73	231	286	3,620	1,463	2,133	54.8
	Average....	80	258	299	3,953	1,882	2,349	54.6

* Ten per cent. added for the specific dynamic action of food, and 15 per cent. for additional movements in bed.

carbohydrate intake of this patient, it would indicate that an average of 362 calories, or 9.2 per cent., of the total caloric intake were lost daily in the feces. This seems to be a fair estimate of the average amount of food lost in the stools in patients with exophthalmic goiter who are consuming a high calorie diet; and hence this value, based on the observations of Müller and Hirschlaff, has been used. Another

10. Müller, Friedrich, and Hirschlaff, W., quoted by Magnus-Levy in Von Noorden, C.: Metabolism and Practical Medicine, Chicago, W. T. Keener & Co. **3**:1000, 1907.

possible source of energy loss, in some patients with this disease, is a glycosuria which may be of importance. In this patient repeated examinations of the urine did not show the presence of sugar. The food which was stored as body tissue is represented in this patient by a gain in weight of 3.4 kg. As glycogen is not stored in an appreciable amount, it is inferred that this gain in body weight must be represented by deposits of fat and protein. As the chemical studies were incomplete in this case, it is impossible to state the exact proportion of these two food elements which were stored. Judging from the studies in Hirschlaff's [8] case, it would be approximately correct to assume that 50 per cent. was stored as fat and 50 per cent. as protein. A deposition of 1.7 kg. of fat and a like amount of protein over a period of twenty-eight weeks would represent a caloric value of 132 calories daily. A summary of the caloric intake and expenditure for the twenty-eight weeks' observation period is presented in Table 3.

TABLE 3.—*Summary of Caloric Intake and Energy Expenditure for One Hundred and Ninety-Six Days*

Average daily caloric intake	3,953
(Protein, 80 gm.; fat, 258 gm.; carbohydrate, 299 gm.)	
Computed energy expenditure	2,349
(Basal metabolism plus 25 per cent.)	
	1,604
Calories lost in feces daily (estimate)	362
	1,242
Calories stored as fat and protein daily (estimated)	132
	1,110*

* One thousand one hundred and ten equals 59 per cent. of average basal metabolism.

As all known sources of energy expenditures have been considered, as indicated in Table 3, it must necessarily be deduced that the balance of 1,110 calories, which constitutes 59.0 per cent. of the average daily basal metabolism, must have been consumed in the almost incessant, semipurposeful movements, which are so characteristic of a patient with exophthalmic goiter. It appears, therefore, from the data just submitted that an allowance of 15 per cent. for additional movements while in bed is an insufficient amount by 59 per cent. of the basal metabolism. In calculating the dietary requirements of a patient with exophthalmic goiter, therefore, it is necessary to add to the basal metabolism, 10 per cent. for the specific dynamic action of food, and 74 per cent. for movements while at "complete rest" in bed, or a total of 84 per cent. This conclusion is in approximate agreement with the conclusions of Boothby,[9] who suggests that at least 75 per cent. be added to the basal metabolism to meet the dietary requirements in this disease.

It is interesting to note the huge quantity of food which these patients are able to consume and apparently utilize. From April 5 to May 31, a period of fifty-six days, the paitent's average daily caloric intake

was 5,254. The lowest average daily caloric intake during any one week of this time was 4,777, while the highest was 5,723. During this period the paitent's body weight increased from 44.8 kg. to 56.5 kg., a gain of 11.7 kg. The ingestion of such a large amount of food by a woman varying in weight from 44.8 kg. to 56.5 kg. and resting in bed, seems all the more remarkable when compared to the calories necessary for a man of 70 kg. who is doing hard work, which Voit estimates at 3,574 per twenty-four hours, Rubner at 3,362 per twenty-four hours and Atwater at 4,150 for a similar period.[11]

IMMEDIATE AND SUBSEQUENT EFFECTS OF AN ACUTE TONSILLITIS

After the patient had remained in the hospital eleven days, at which time the metabolic rate had fallen to 49 per cent. above the average normal, an acute attack of tonsillitis developed which manifested itself by fever as high as 103 F., and reddened, swollen tonsils which were covered by a moderate amount of exudate. The patient's temperature was elevated from 8 p. m. on March 12 until midnight on March 17, a period of approximately five days. The highest temperature during this time was 103 F., and the lowest was 99.8 F., while the average was approximately 101 degrees.

The observations on the temperature, metabolism, pulse rate, food intake, and loss of weight during this illness are of interest from two standpoints: (1) the immediate effect of an acute infection on a patient with exophthalmic goiter, and (2) the influence of the acute infection on the subsequent course of the thyroid disturbance.

Immediate Effect of an Acute Infection.—It has been observed by DuBois and his co-workers [12] that with an increase in body temperature, the basal metabolism rises, in a definite relationship to the temperature. If the temperature remains elevated and the food intake is not increased a proportionate amount, the patient will of course consume his own tissues and lose in body weight. This applies also to a patient with exophthalmic goiter, but in this disease the situation is more of a strain on the heat regulating and nutritive systems of the body as the increase in metabolism, which results from fever, is an increment which must be added to an already elevated metabolism due to the preexisting exophthalmic goiter. In the patient under observation, the heat production increased sharply from 49 per cent. to 104 per cent. above normal, as the fever rose from normal to 102.2 F. (by mouth). Thereafter for a pariod of five days the metabolism remained elevated, but maintained a definite relationship to the degree of fever, as shown in Table 4.

---

11. Lusk, Graham: The Science of Nutrition, Ed. 3, Philadelphia, W. B. Saunders Company, 1921, p. 350.

12. DuBois, Eugene F.: The Basal Metabolism in Fever, J. A. M. A. **77**: 352 (July 30) 1921.

With the marked rise in the metabolism associated with the fever, the patient's appetite failed; hence there was a diminution in the caloric intake. From the patient's admission until the onset of the acute tonsillitis (eleven days), the patient's average daily food consumption had been approximately 2,500 calories, and despite this her weight had decreased from 52.6 kg. to 49.0 kg., a loss of 3.6 kg. During the five days in which the patient had fever, her food intake diminished to an average of 1,199 calories daily. The patient, therefore, had the undesirable combination of an increased energy expenditure associated with a decreased food intake. The result was a decrease in body weight from 49 kg. to 46.4 kg. (2.61) in five days. This weight loss, when added to the amount the patient had lost during the eleven days previous to the onset of the acute tonsillitis, amounted to 7.2 kg. (approximately 16 pounds) in sixteen days. This illustrates one strik-

TABLE 4.—*Relationship Between the Body Temperature and the Basal Metabolism*

Day of Month	Temperature (by Mouth) Taken at the Time of the Metabolism Determination	Basal Metabolism per Cent. Above Average Normal
March 12	98.0	49
13	102.2	104
14	102.0	91
15	101.4	90
16	100.5	75
17	99.4	65
18	98.6	58

ing and immediate effect of an acute infection in a patient with exophthalmic goiter. Furthermore, an additional strain is thrown on the heat regulatory apparatus of the body, which is obliged to deal with the elimination of a large excess of heat owing to a combination of the increased heat production as a result of the exophthalmic goiter and that due to the fever. This patient during the febrile period seemed very drowsy, suffered greatly from a feeling of warmth and appeared "toxic."

INFLUENCES OF THE ACUTE TONSILLITIS ON THE SUBSEQUENT COURSE OF THE THYROID DISTURBANCE

Recently Squire [13] has reported two cases of exophthalmic goiter, in which both patients manifested great improvement subsequent to attacks of acute tonsillitis. The most striking change was the remarkable increase in weight, one of the patients gaining 56 pounds (25.4 kg.) and

13. Squire, Theodore S.: Improvement in Graves' Disease Subsequent to Severe Focal Infection, Am. J. M. Sc. **160**:358, 1920.

the other 115 pounds (52.16 kg.) in approximately six months. It was thought by this observer that probably the improvement resulted either from invasion of the thyroid gland by infection with subsequent loss of secretory tissue or as a result of glandular exhaustion.

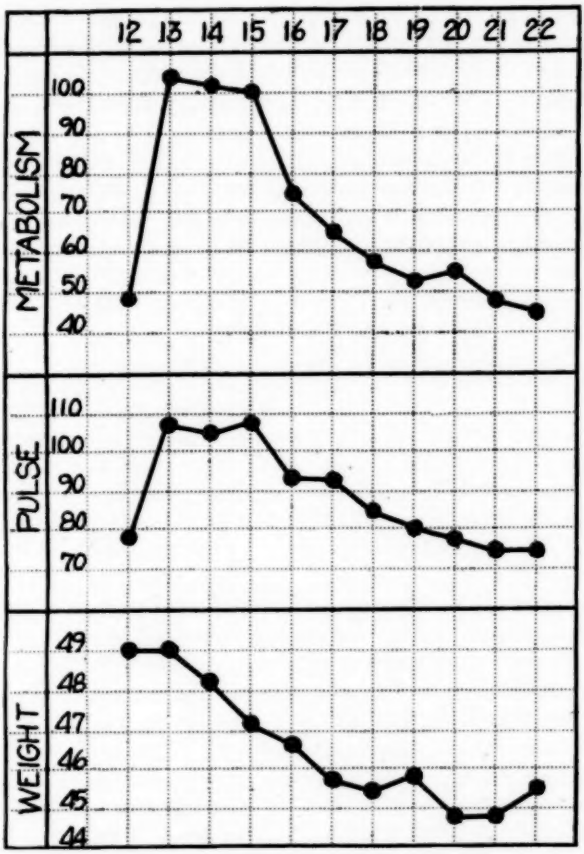


Chart 3.—The effect of an acute tonsillitis with fever on the daily basal metabolism, resting pulse rate and body weight. The patient developed fever on the thirteenth of the month, which persisted until the seventeenth. The increase in the metabolism was approximately proportional to the degree of fever. The changes in the resting pulse corresponded to the variations in the basal metabolism. The decrease in body weight resulted from an increase in the metabolism and a diminished food intake.

An excellent opportunity was afforded to observe the subsequent results of an acute tonsillitis in the patient who was studied in this instance, as she was under observation for a period of 185 consecutive

days after the acute infection and has been seen at weekly intervals since then. Following the acute tonsillitis the patient's metabolism returned approximately to its previous level (+ 49) as soon as the temperature became normal. Subsequent to this, for a period of 130 days, it remained in the vicinity of 40 per cent. above the average

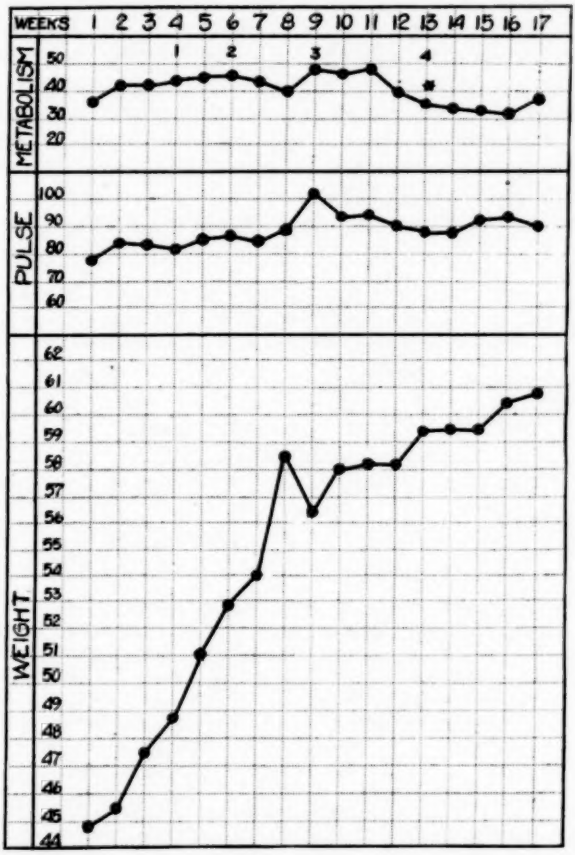


Chart 4.—The average basal metabolism, pulse rate and body weight per week for seventeen weeks, from March 25 to July 29. The figures just above the metabolism curve indicate the times at which the four roentgen-ray treatments were given. The star represents the interval of six days when the patient was permitted to go home for six days. The only significant change shown in the chart is a gain of 16 kg. in body weight. This is not interpreted as evidence of the beneficial effect of the roentgen-ray treatment, but was coincident with the development of an increase in appetite which permitted the patient to consume a large amount of food.

normal, while the pulse maintained a constant level of approximately 80 per minute. After the patient had been afebrile for four days, there was a great improvement in her appetite and from between 5,000 and 6,000 calories of food were consumed daily. As a result of this increased food consumption there was a gain in body weight of 16.3 kg. in 121 days. The upward course of the weight curve began thirteen days after the period of fever and continued steadily until the peak was reached, 121 days later. For twenty-seven days following the febrile period the patient did not receive any treatment other than rest in bed and a high caloric diet. At the end of that time, however, the initial roentgen-ray treatment was given, and this was followed at intervals of approximately three weeks by three more, making in all four treatments. In summary, therefore, it might be said, that following the

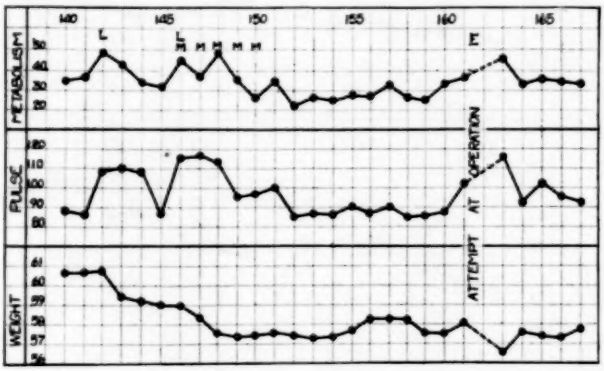


Chart 5.—The effect of ligation of two thyroid arteries on the basal metabolism, pulse rate and body weight. The metabolism is expressed in percentage of normal, the pulse in beats per minute, and the body weight without clothing in kilograms. *L*, indicates ligation of a thyroid artery; *M*, days during which the patient was menstruating; the figure at the top of the chart indicates the number of days the patient had been in the hospital; *E*, the day on which the patient was completely anesthetized but not operated on on account of the unfavorable reaction following the administration of the ether.

attack of acute tonsillitis the only change in the patient's condition was a gain of 16.3 kg. in body weight in 121 days, while the pulse rate and metabolism remained unchanged. It seems unlikely that the enormous appetite, which caused the patient to consume such an excess of food, can be attributed to the influence of the acute infection on the thyroid gland. Furthermore, it seems logical to assume that a gain in body weight such as this, if it was due either to exhaustion of the thyroid gland or to actual destruction of a portion of its secretory tissue, would be accompanied by a reduction in the basal metabolism and pulse

rate, which in this case did not occur. Concerning this patient, therefore, it must be concluded that there is no clear evidence which indicates that the attack of acute tonsillitis exerted any influence on the subsequent course of the disease.

THE EFFECT OF ROENTGEN-RAY THERAPY

The influence of roentgen-ray treatment has been tried on a relatively small group of patients with exophthalmic goiter at this hospital, and the conclusions regarding the efficacy of this mode of treatment are not as yet permanent. A certain proportion of patients have made a satisfactory recovery following the use of this therapeutic agent. Even the most enthusiastic advocates of its use agree, however, that in some instances the patient fails to respond to this therapy even after prolonged and intensive use. Why some will and others will not improve following its use, has not been decided. The patient under observation apparently belonged to the group that does not respond, as four

TABLE 5.—*The Effect of Four Roentgen-Ray Treatments on the Basal Metabolism*

	Dates	Days	Average Metabolism	Amount Gained in Body Weight, Kg.
I. Observation period.....	March 23 to April 14	23	+46	1.6
II. Roentgen-ray treatments.....	April 15 to June 12	59	+45	9.6
III. Observation period following treatments	June 13 to July 27	44	+40	2.7

roentgen-ray treatments at intervals of about three weeks had no apparent affect on the course of the disease. The first treatment was given after the patient had been resting in bed in the hospital for forty-five days. For the twenty-three days previous to the initial roentgen-ray treatment the average basal metabolism had been + 46 per cent., while the maximum and minimum determination were + 39 per cent. and + 52 per cent. When the daily metabolism results were charted, it was evident that the metabolic rate for these twenty-three days had struck a level, as there was no upward or downward tendency of the curve. The roentgen-ray treatments were given over an interval of fifty-nine days, during which time the average metabolism was + 45, and the resting pulse rate showed no change of level. An additional period of forty-four days was allowed, following the fourth roentgen-ray exposure, to observe the effect of the treatment. The patient was inclined to think that she was "stronger" and was optimistic about her condition. The results of the metabolism determination and gain in body weight are shown in Table 5.

The interval including periods 2 and 3, a total of 103 days, was thought sufficient to observe the effect of roentgen-ray therapy. As shown by the table, there was no marked change in the average metabolic rate for the periods as 5 per cent. is considered a permissible error, and the difference between the daily average in period 1 and period 2 is 5.8, a decrease which cannot be regarded as significant. The only evidence of improvement in the patients condition is the substantial gain of 12.3 kg. in body weight. This, however, cannot be used as convincing evidence of the action of the roentgen rays on the thyroid gland, as one would expect a gain in body weight due to this influence to be associated with a decreased metabolism.

THE EFFECT OF SURGICAL PROCEDURES

After the patient had been in the hospital for 148 days and her condition had remained stationary over a long interval despite rest, forced feeding and four roentgen-ray treatments, surgery was used as a therapeutic measure. On July 27, the one hundred and forty-eighth day of observation, the left superior thyroid artery was ligated under local anesthesia by Dr. John Homans of the surgical staff of this hospital, and four days later the same procedure was carried out on the right side. Four days after the second ligation the metabolism fell to + 27 per cent., which was the first time in 157 days of observation that it had been so low. The average metabolism for the ten days immediately following the ligation was + 27, and the minimum was 6 per cent. below this. Following this transient drop, however, it again resumed its former preoperative level between + 30 and + 40 per cent. above normal. Hence the improvement which followed the two ligations, as indicated by the decreased basal metabolism, was transient and slight. Sixteen days after the second ligation an attempt was made to perform a lobectomy, but the administration of the anesthetic was accompanied by such an alarming increase in the patient's pulse rate that the attempt was abandoned for that day. It is interesting to note that the patient's metabolism on the day following the complete anesthetization was + 45 per cent., a rise of only 9 per cent. above the basal metabolism on the day previous to administration of the anesthetic.

Six days after the attempted lobectomy the patient was operated on under local anesthesia by Dr. John Homans. During the operation the patient's condition again became precarious, and it was only possible to remove approximately one half of the thyroid gland as further surgical procedure at this time was not considered justifiable. About two hours after the operation the patient's condition had improved considerably, and it was possible to collect the expired air for a single period of six minutes. The basal metabolism for this period was found to be + 79 per cent. A seven-minute period the following day showed

the metabolism to be + 75 per cent. For the following two days, the patient's condition was so serious that it was not considered wise to attempt metabolism determinations. On the fourth day after operation, the metabolism estimations were resumed, and from this time until the patient left the hospital, the average was as follows: first week, + 26 per cent.; remaining nine days of the patient's stay in the hospital, + 32 per cent. The first obvious drop following the lobectomy occurred on the fifth day after operation when the metabolism was found to be + 21 per cent., while the lowest level of metabolism, which was + 13 per cent., occurred on the thirteenth day following operation. The metabolism remained at a comparatively low level for seven days, then gradually rose to a level between + 25 and + 30 per cent. and

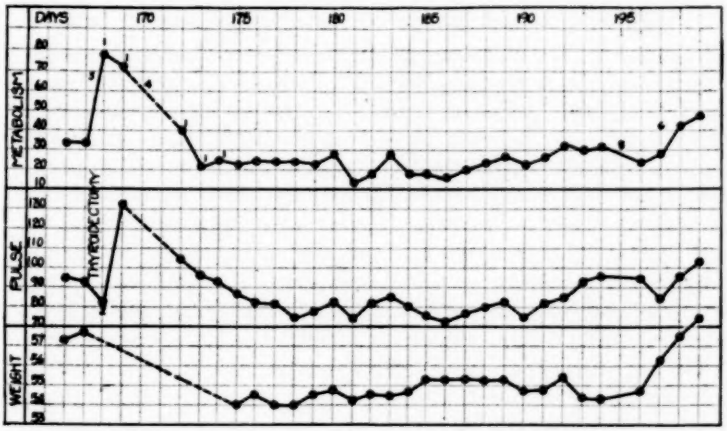


Chart 6.—The effect of removal of approximately one half of the thyroid gland on the basal metabolism, resting pulse rate per minute and body weight. 1, the body weight on the day previous to the operation was used in estimating the surface area. 2, the pulse rate at the wrist was 82 per minute while that at the apex of the heart, while not counted, was much higher. The pulse deficit was due to many extrasystoles. 3, about one half of the thyroid gland was removed under local anesthesia. Approximately one hour after the conclusion of the operation the patient's expired air was collected for one six-minute period. 4, the patient was too ill to make metabolism determinations on the second and third postoperative days. 5, determination lost on account of technical error. 6, the last three determinations on the chart were made after the patient had returned home and was resting about half of the time in bed. She came to the hospital at weekly intervals for observation.

remained at this point during the remainder of her stay in the hospital. The patient was discharged from the hospital on September 19, the two hundred and second day of observation, and the twenty-eighth after operation.

After leaving the hospital the patient remained at home resting in bed about half of each day. Weekly observations were made on her metabolism between September 19 and November 10. During this interval, her pulse rate and metabolism reached a level varying between 90 and 102 per minute for the former and between + 38 per cent. and + 47 per cent. for the latter. There was a gain in weight of 3.7 kg. during this period. As the patient's condition was not improving, it was decided that a second operation was necessary to remove more of the thyroid gland. On November 13, Dr. David Cheever of the surgical staff performed this operation using local anesthesia. The patient made an uneventful recovery and on the sixth post-operative day her metabolism was found to be + 14 per cent. and her pulse rate 66 per minute. It seems assured that her condition will continue to remain satisfactory.

EFFECT OF MENSTRUATION ON THE BASAL METABOLISM

Little is known concerning the effect of menstruation on the basal metabolism in normal women, or in women with exophthalmic goiter. Snell, Ford and Roundtree [14] refer to this subject and state that it may be of some practical clinical importance. These investigators studied the basal metabolism during the menstrual periods of ten normal women and drew the following conclusions concerning them: Two showed practically constant rises, while six showed constant rises, varying from 4 per cent. to 14 per cent., the average being 10 per cent., while in two a drop in rate was encountered. The rise, when it occurs, is in the menstrual or premenstrual period and is followed by a postmenstrual fall. Values outside of normal limits (10 per cent. above or below the average normal) were infrequent.

The patient who was observed during this study passed through seven menstrual cycles. Each period varied from five to six days, and was not accompanied by pain or other subjective sensations. Chart 7 indicates the metabolic rate during six periods. The metabolism during the seventh menstrual period was influenced by lobectomy, so no definite conclusion could be deduced. The first menstrual period occurred in the initial two weeks of the patient's stay in the hospital, and it was during this interval that the greatest fluctuations were present in the metabolism. It is, therefore, exceedingly difficult to estimate the influences of any factor on the metabolism at this time. The second and third menstrual periods showed a curious agreement in their fluctuations. If the rise which occurred on the first day of these periods is due to the appearance of the menstrual function, it is a small increase, as it amounts to only 5 per cent., which is just the limit of error. The fall

14. Snell, A. M.; Ford, Francis, and Roundtree, L. G.: Studies in Basal Metabolism, J. A. M. A. **75**:515 (Aug. 21) 1920.

on the second day of the menstrual period in these curves is of greater extent as it amounts to approximately 10 per cent. Curves 4 and 5 of the fourth and fifth menstrual periods do not confirm the changes observed in curves 2 and 3. Curve 6 cannot be used as on the initial day of the menstrual function the right superior thyroid artery was

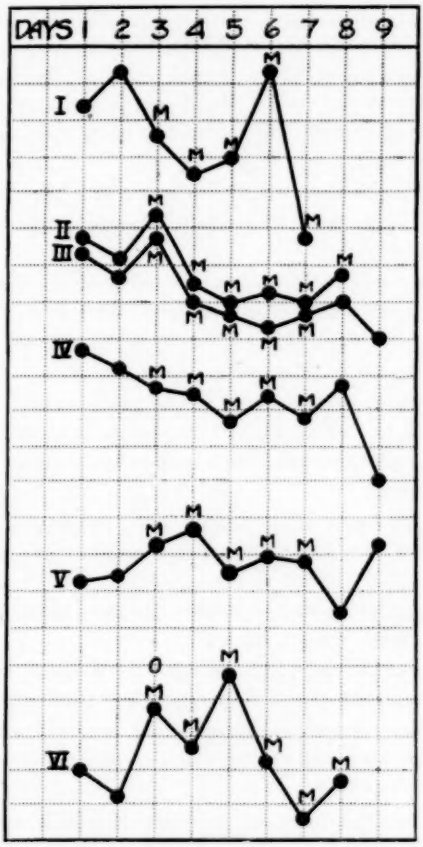


Chart 7.—The effect of the menstrual cycle on the daily basal metabolism. The metabolism is charted for each day for an interval varying from seven to nine days during the six menstrual periods which the patient passed through while under observation. Each space in a perpendicular direction represents a change of 5 per cent. in the metabolism. *M*, represents days when patient was menstruating; *O*, ligation of the right superior thyroid artery. The first cycle occurred shortly after the patient was admitted, when her condition was very unstable. The sixth was influenced by ligation of the right superior thyroid artery. From the foregoing observations it was concluded that menstruation had no effect on the basal metabolism.

ligated, which in itself is sufficient to account for the rise in metabolism on that particular day and for the subsequent fluctuations. From the observations on this patient, therefore, it must be concluded that the metabolic rate was slightly, if at all, influenced by the menstrual function.

CONCLUSIONS

A patient with exophthalmic goiter was observed while at rest in bed in the hospital from March 1, 1922, to September 19, 1922, an interval of approximately six and a half months. During this time the basal metabolism, resting pulse, food intake and body weight were determined practically every day. The following conclusions have been drawn from this study:

1. The basal metabolism may be determined within a limit of 5 per cent. error, and in a great majority of instances this error may not exceed 3 per cent.

2. The initial metabolism of a patient with exophthalmic goiter may be much higher than the subsequent metabolism, and even after a rest in bed of ten days the fluctuation in the metabolism from one day to the next may be as great as 23 per cent.

3. After a rest of several weeks in bed there was a tendency for the basal metabolism in this particular patient to be come stabilized, and for a period of several months the variation on consecutive days rarely exceeded 5 per cent.

4. The body weight of a patient with exophthalmic goiter may remain stationary, increase or decrease, irrespective of the level of the basal metabolism, dependent on the amount of food consumed. Most frequently the appetite of such a patient is good or abnormally increased; despite this, the body weight decreases.

5. The number of calories adequate to maintain a patient with exophthalmic goiter in caloric balance, when resting in bed, may be estimated as approximately an 85 per cent. increase over the number of calories which represent the patient's basal metabolism for twenty-four hours.

6. Acute infections, such as an acute tonsillitis with fever, may exert a serious influence on a patient with exophthalmic goiter, owing to the great excess of heat produced and the large amount of weight which is lost as a consequence of a high basal metabolism and a small food intake. In this particular patient no beneficial effect as a result of the acute tonsillitis was observed in the subsequent course of the thyroid gland disorder.

7. The menstrual periods did not exert an appreciable effect on the basal metabolism in this patient.

8. Four roentgen-ray treatments over the thyroid gland at intervals of three weeks had no effect on the course of the disease.

9. Ligation of two thyroid arteries was followed by a transient drop in the daily basal metabolism, and removal of approximately half of the gland had a similar effect.

THE EFFECT OF ALKALIS ON GASTRIC SECRETION AND MOTILITY AS MEASURED BY FRACTIONAL GASTRIC ANALYSIS

BRUCE C. LOCKWOOD, M.D., AND HAZEN G. CHAMBERLIN, M.D.
DETROIT

The object of this work was to determine by fractional analysis, in a sufficiently large number of persons, two points: (1) whether or not alkalis in addition to their immediate neutralizing effect also produce a secondary rise of acidity greater than that which occurs in a person without their administration; (2) what effect alkalis have on gastric motility.

Without extensively quoting the early literature on the subject, it is sufficient to state that there has always been a difference of opinion as to whether alkalis act as a stimulant or depressant to gastric secretion. The defenders of the alkaline Spa treatments held that while at times an alkali might act as a stimulant shortly after taking, the prolonged administration caused a gastric catarrh with associated decreased secretion. Those who believed that alkalis acted only as a depressor of gastric secretion were supported by Pawlow's observation [1] that on a dog, soda produced a diminution of all the alimentary secretions.

On the other hand, many early French and German investigators, especially the clinicians, held that alkalis in any dosage acted only as a stimulant.

The more recent textbooks and articles dealing with this subject reflect the different views, although we could find no one investigation in which accurate methods were used on a sufficiently large number of subjects to draw definite conclusions.

Cushny [2] states that it has been demonstrated experimentally on dogs that alkaline carbonates do not influence the gastric secretion any more than free water. Gross and Held [3] say that alkalis before or with meals increase acidity. Hemmeter [4] does not believe that alkalis increase secretion, but that if they are taken before meals, they may act as a temporary irritant, just as saline in the nose would excite a mucous flow. Bassler [5] thinks that alkalis do not stimulate secretion and may be kept up for long periods of time without harm.

---

1. Pawlow: The Work of the Digestive Glands, Philadelphia, J. B. Lippincott Co., 1910.
2. Cushny, A. R.: Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1915.
3. Gross, M. H., and Held, I. W.: Therapeutics of the Gastro-Intestinal Tract, New York, Rebman Co., 1913.
4. Hemmeter: Diseases of the Stomach, Philadelphia, P. Blakiston's Son & Co., 1917.
5. Bassler, A.: Diseases of the Stomach and Upper Alimentary Tract, Philadelphia, F. A. Davis Co., 1917.

Crohn,[6] with the fractional method, investigated the action of different doses of bismuth subnitrate, magnesium oxid, and sodium bicarbonate, given at different times in relation to the test meal. His conclusions, however, are based on only one or two observations with any one method of administration and should be accepted with reserve in view of the variations which one sees in the response of the stomach at different times. He states that the administration of either soda or magnesia is followed by an irritative reaction in which the acid mounts quickly to at least the level of the control test at the corresponding time, and in most cases exceeds it.

Fowler, Spencer, Rehfuss and Hawk [7] state that the stomach tends to bring its contents to a normal acid level, regardless of the reaction of ingested substances, that is, it lowers acidity when strong acids are introduced, and raises acidity when alkalis are given.

Regarding the effect of alkalis on motility, the literature is scanty. Ladd,[8] experimenting on a series of children, found that bismuth and other alkalis hastened the emptying time of the stomach. Spencer, Meyer, Rehfuss and Hawk [9] found that 5 per cent. soda solution was held in the stomach until reduced, and that a 1 per cent. solution hastens the emptying time. Carlson reports [10] that 1 per cent. sodium carbonate solution inhibits gastric contractions for a short time, as water does, and is due to the bulk of the solution.

METHOD OF PROCEDURE

The method employed in the following experiments is identical with that used in previous work, reports of which have been published.[11] The subject on a morning fasting stomach swallowed the small fractional tube, and the fasting contents were aspirated. An Ewald meal was then given with the tube left in place and from 5 to 10 c.c. were aspirated every fifteen or twenty minutes.

When the return was free from bread, this point was taken as the evacuation time. The free and total acidity was determined by the Toepfer method. All patients had been previously tube broken. The

6. Crohn, B. B.: Effect of Antacid Medication on Gastric Secretion and Acidity, Am. J. M. Sc. **155**:801, 1918.

7. Fowler, C. C.; Spencer, W. H.; Rehfuss, M. E., and Hawk, P. B.: Gastric Analysis. IV. The Gastric Equilibrium Zone, J. A. M. A. **77**:2118 (Dec. 31) 1921.

8. Ladd: Influence of Alkalies on Gastric Motility, Boston M. & S. J. **170**:518, 1914.

9. Spencer, W. H.; Meyer, G. P.; Rehfuss, M. E., and Hawk, P. B.: Am. J. Physiol. **39**:459, 1916.

10. Carlson, A. J.: Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916.

11. Lockwood, B. C., and Chamberlin, H. G.: The Effect of Olive Oil on Gastric Function as Measured by Fractional Analysis, Arch. Int. Med. **31**:96 (Jan.) 1923.

normal curve, and the curve after the administration of alkali were all taken within a few days of each other and an effort made to keep the subject on the same general routine, diet and water intake. In securing the test curves, the alkali was given in the water of the test meal.

RESULTS

Sodium Bicarbonates.—The effect of administration of 4 gm. doses of this drug, given with the test meal, was observed on eight carefully controlled cases. The average free hydrochloric acid was higher than the control in only one case, while the general average for the series was reduced from 40.6 degrees in the controls to 31.7 degrees after the soda. The average total acidity was higher than the control in two cases, while the average for the series was reduced from 54.8 degrees to 44.1 degrees after the soda. The free hydrochloric acid rose to a

TABLE 1.—*Results of Administration of 4 gm. of Sodium Bicarbonate with the Ewald Meal in Eight Cases*

Case	Average Free Acid		Average Total Acid		Maximal Free Acid		Maximal Total Acid		Evacuation Time		Bile	
	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control	Test	Control	Test
G. S.	36	60.2	54.1	72.9	60	98	80	104	80	120	0	+
F. M.	22	18.7	29.4	27	40	42	50	60	100	100	0	0
A. D.	40	16.1	52	22.3	51	25	66	32	120	120	0	0
J. M.	37	35.5	54.2	51.2	56	60	72	80	100	120	0	0
P. G.	37.2	37.1	42	47.2	63	60	70	76	120	80	0	0
H. G.	51.2	37.8	67.7	52.8	60	73	78	88	105	75	+	0
A. G.	43.7	17.7	65	22.7	72	40	93	46	135	75	0	0
A. S.	58.2	30.6	74	47.2	78	55	97	73	135	135	0	0
Average..	40.6	31.7	54.8	44.1	.....	.....	.....	.....	112	103		

higher point on the curve after the administration of soda than in the control in four, or one-half, of the total eight cases. The total acidity attained a higher point in five cases.

The average evacuation time in the controls was 112 minutes, while after soda, it was 103 minutes, only a slight reduction. Bile regurgitation was observed in one control curve and in one curve after the administration of soda. Table 1 shows these results in convenient form.

In Chart 1 are plotted five total acidity curves on the same patient (H. G.—duodenal ulcer). All these observations were made within two weeks. The two control curves (dotted) run practically the same. Two curves are shown in which 4 gm. of sodium bicarbonate were given with the test meal. One remained low while the other rose within forty-five minutes to about the same maximal height as the control curves. One curve (No. 3) shows a case in which 4 gm. of soda were given thirty minutes after the meal. The acid promptly dropped, but within another thirty minutes had risen to about the same level as in the controls, to fall slowly again as digestion proceeded.

Calcium Carbonate.—In this series of six cases, 4 gm. of the drug were given with the meal and comparison made with the control curves.

The average free hydrochloric acid was lower after the alkali in all observations, and for the series was reduced from an average of 32.1 degrees in the control curves to 11.9 degrees after the calcium carbonate. The average total acidity was higher after the drug in two cases, but the average for the series was reduced from 54.8 degrees in the controls to 44.1 degrees after the calcium carbonate. The free hydrochloric acid attained a higher point in two cases, and the total acidity in three cases, after the medication than in the six corresponding control curves.

The average evacuation time was almost the same, 100 minutes for the controls and 103 minutes for the calcium carbonate. Bile was seen

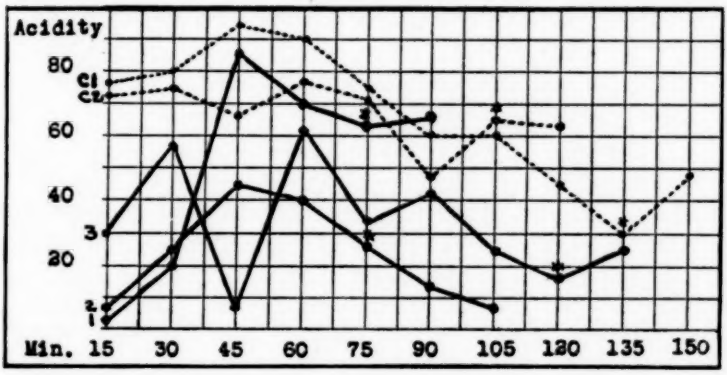


Chart 1.—Acidity curves in subject H. G. *C1* indicates the control curve on January 21; *C2*, the control curve on January 30; *1*, the curve after 4 gm. of sodium bicarbonate were given with the Ewald test meal on January 24; *2*, the curve on January 30 after the same test; *3*, one-half hour after ingestion of the Ewald test meal. The star in this and the following charts indicates that bread was absent.

in one curve after medication and in none of the controls. Table *2* shows these results.

Magnesium Oxid.—With this alkali the effects were observed in five cases. Two grams were given with the meal.

The average free hydrochloric acid was lower in all cases, and the average for the series was reduced from 35.3 degrees in the controls to 15.5 degrees after the administration of the magnesia.

The average total acidity was also lower in every observation and for the series was reduced from 50.5 to 20.2 degrees.

The free hydrochloric acid and also the total acidity rose to a higher point after this alkali in only one of the five cases. The average

evacuation time was exactly the same; 104 minutes in both the control and test observations. Bile was observed once in the test curves and not at all in the control curves. In Table 3 these results are tabulated.

TABLE 2.—*Results of Administration of 4 gm. of Calcium Carbonate With the Ewald Meal in Six Cases*

Case	Average Free Acid		Average Total Acid		Maximal Free Acid		Maximal Total Acid		Evacuation Time		Bile	
	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control	Test	Control	Test
G. S.	36	1.3	54.1	9.3	60	8	80	18	80	100	0	+[a]
A. D.	40	20.8	52	27.2	51	76	66	82	120	120	0	0
P. G.	37.2	34.3	42	41.0	68	78	70	86	120	100	0	0
M. M. K.	42.6	9.4	62.3	18.4	67	32	77	43	80	100	0	0
S. W.	Ach'lia	....	2.5	4.9	0	0	5	10	100	100	...	0
B. M.	37	6.1	54.2	18.6	56	25	72	42	100	100	0	0
Average..	32.1	11.9	44.5	19.8	.....	.....	.....	.....	100	103		

TABLE 3.—*Results of Administration of 2 gm. of Magnesium Oxid with the Ewald Meal in Five Cases*

Case	Average Free Acid		Average Total Acid		Maximal Free Acid		Maximal Total Acid		Evacuation Time		Bile	
	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control	Test	Control	Test
A. L.	26.4	21.6	50.4	33.4	35	58	54	88	100	120	0	0
P. G.	37.2	6.0	42	17.7	63	24	70	54	120	80	0	+[a]
J. M.	37	10.8	54.2	22.0	56	36	72	48	100	100	0	0
A. D.	40	15.6	52	20.5	51	60	66	66	120	120	0	0
G. S.	36	23.4	54.1	27.4	60	50	80	57	80	100	0	0
Average..	35.3	15.5	50.5	20.2	.....	.....	.....	.....	104	104	0	0

TABLE 4.—*Results of Administration of 4 gm. of Bismuth Subnitrate with the Ewald Meal in Seven Cases*

Case	Average Free Acid		Average Total Acid		Maximal Free Acid		Maximal Total Acid		Evacuation Time		Bile	
	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control	Test	Control	Test
G. S.	36	63.8	54.1	70.5	60	84	80	88	80	80	0	0
J. M.	37	29.9	42	39.4	63	40	70	50	120	80	0	0
A. D.	40	23.1	52	36.7	51	30	66	43	120	100	0	0
A. L.	26.4	16	50.4	26.6	35	30	54	44	100	120	0	0
M. K.	42.6	39	62.3	50.6	67	56	77	70	80	100	0	0
H. G.	51.2	73.5	67.7	90.9	60	90	78	97	105	135	+[a]	0
P. G.	37.2	26	42.2	38.1	63	34	70	45	120	100	0	0
Average.	38.6	38.7	52.9	50.4	.....	.....	.....	.....	103	102		

Bismuth Subnitrate.—The effect of this drug was studied in seven cases. A dose of 4 gm. was given with the meal in each test.

The average free hydrochloric acid, total acidity and evacuation time were practically the same before as after its administration. The free

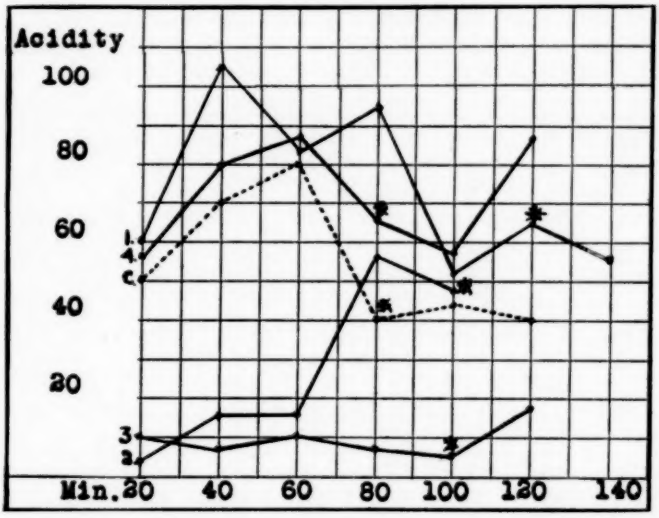


Chart 2.—Effect of four alkalis on subject G. S. In this and the following charts, *C* indicates the control curve after the ingestion of the Ewald test meal; *1*, the curve after the ingestion of 4 gm. of soda with the test meal; *2*, after the ingestion of 2 gm. of magnesium oxid with the test meal; *3*, after the ingestion of 4 gm. of calcium carbonate with the test meal; *4*, after the ingestion of 4 gm. of bismuth subnitrate with the meal.

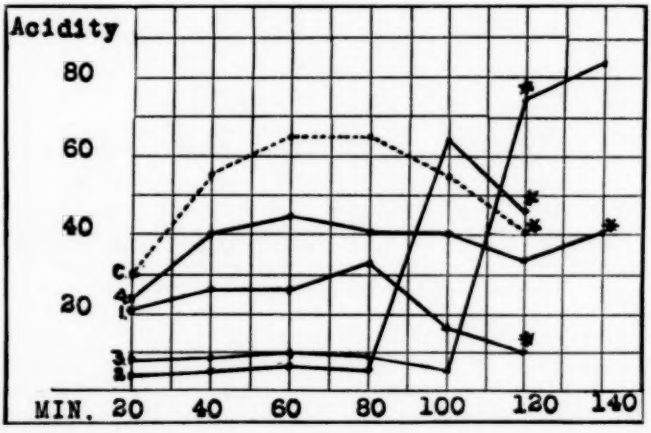


Chart 3.—Effect of four alkalis on subject A. D.

and total acidity both rose to a higher point in only two of the test curves. Bile was seen in one of the control curves and in none of the test curves. These results are shown in Table 4.

The effect of four alkalis on the curve of the same person are shown for four different subjects. Charts 2, 3, 4 and 5 each show a control

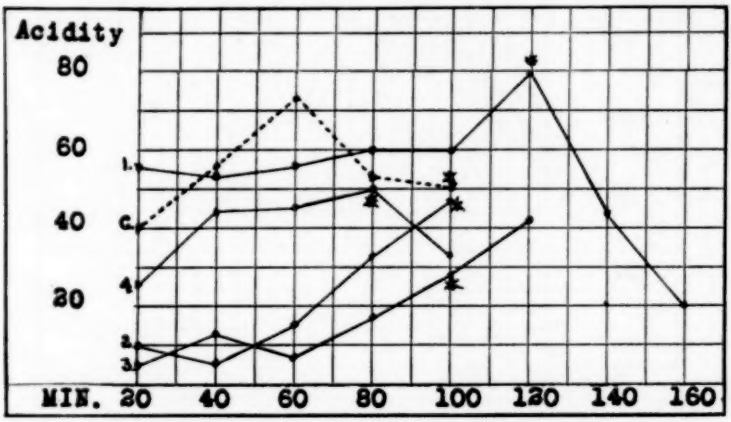


Chart 4.—Effect of four alkalis on subject J. M.

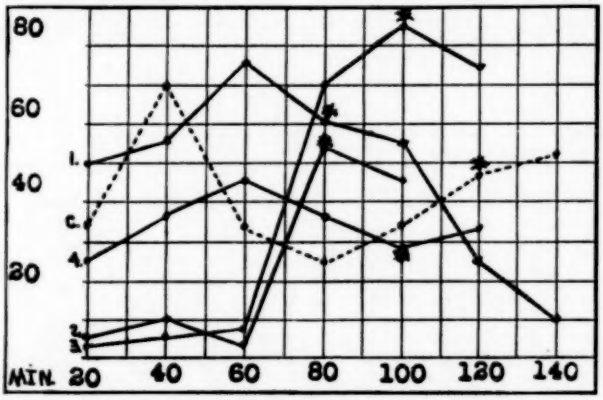


Chart 5.—Effect of four alkalis on subject P. G.

curve of total acidity (dotted) on four different persons assumed to be free from gastro-intestinal disease. With each control are also shown curves obtained after the administration of the four different alkalis studied. These curves are self explanatory. They were all taken within one week.

SUMMARY AND COMMENT

The effect on gastric function of the administration of a standard dose of four different alkalis is studied. They were all given with the Ewald meal and comparison made with control curves in twenty-six cases.

Neither sodium bicarbonate, calcium carbonate, magnesium oxid or bismuth subnitrate seemed to affect the evacuation time of the stomach. This does not support Cannon's [12] conception of the acid control of the pyloris. The phenomenon of bile regurgitation was also unaffected.

The average free and total acidity was lower after the administration of the alkali in all observations on calcium carbonate and magnesium oxid. In less than one fourth of the sodium bicarbonate tests it was higher. The average acidity was unaffected by bismuth subnitrate.

After sodium bicarbonate the acidity rose to a higher point than in the controls in about one half of the cases; after calcium carbonate, in one fourth; and after magnesium oxid, in one fifth of the cases. After bismuth, the acidity attained a higher point in only two of seven cases.

As the neutralizing power of soda is about one half that of calcium carbonate and one fourth that of magnesium oxid, it is apparent that the dose of soda which we used (4 gm.) was only one half as strong a neutralizer as was our dose of calcium carbonate (4 gm.) and magnesium oxid (2 gm.). It is possible that with a dose of soda equal in strength to the dose of calcium or magnesium the acid rebound would have been less in evidence. On the other hand, the liberation of carbon dioxid when soda is given may act as a direct stimulant. This point remains to be cleared up.

CONCLUSIONS

Sodium bicarbonate in 4 gm. doses, in addition to its immediate neutralizing effect, causes a rebound of acidity to a point higher than would normally have occurred in about one half the cases. Calcium carbonate (4 gm.) and bismuth subnitrate (4 gm.) produce this effect in only one fourth, and magnesium oxid in only one fifth, of the cases, while the average acidity during the digestive phase following their administration is much lower in seven eighths of the cases.

The common alkalis in the foregoing dosage do not effect the evacuation time of the stomach for the Ewald meal.

---

12. Cannon, W. B.: The Mechanical Factors of Digestion, New York, Longmans, Greene & Co., 1911.

ACUTE LYMPHADENOSIS COMPARED WITH ACUTE LYMPHATIC LEUKEMIA

HAL DOWNEY, PH.D., AND C. A. McKINLAY, M.D.
MINNEAPOLIS

PART I. CLINICAL STUDY *

C. A. McKINLAY, M.D.

Numerous reports are found in medical literature describing groups of cases which, on account of clinical features and blood cell changes, have been thought to be similar to and often confused with acute leukemia. Naegeli [1] mentions cases of sepsis with low total leukocyte counts and relative increase in the lymphocytes, and also acute febrile affections with high absolute lymphocyte counts with atypical forms. It is pointed out that this lymphatic reaction is more confusing where there is also an absolute lymphocytosis with atypical lymphocytes. Further, with a clinical picture of fever, prostration and enlargement of lymph nodes and spleen, it may be impossible to differentiate these cases from leukemia until recovery occurs. Naegeli quotes Türk and others who report cases of angina and streptococcus sepsis with lymphatic reaction and recovery, besides cases of acute infection, such as pneumonia, scarlet fever, erysipelas, meningitis, typhus and malaria, in which the blood picture showed frequent myelocytes, erythroblasts and severe anemia. Türk considered that there was some relationship between infection with lymphatic reaction and leukemia. Herz [2] mentions that in certain infections there are cases in which the blood picture simulates a lymphatic leukemia, and only recovery makes the diagnosis clear. Cabot [3] reports four cases of acute infection, including lymphangitis, furunculosis, streptococcus sore throat and cervical adenitis, all of which showed lymphocytosis and might be confused with leukemia. His observations are apparently based more on the clinical than on the blood picture resemblance. Sanders [4] reports a case with fatal Ludwig's angina, lymphocytosis and anemia.

---

* From Students' Health Service and Department of Medicine, University of Minnesota.

1. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Berlin and Leipzig. Vereinigung wiss. Verleger, W. de Gruyter & Co., 1919.

2. Herz, A.: Die akute Leukämie, Leipzig, Franz Deuticke, 1911.

3. Cabot, R. C.: The Lymphocytosis of Infection, Am. J. Med. Sc. vol. 145, p. 335.

4. Sanders, W. E.: The Nature of the Lymphocytosis of Acute Infections, Jour. Lab. Clin. Med. 4:344, 1919.

Some English observers [5] and others, including Morse,[6] apparently consider cases with lymphatic reaction to be similar to glandular fever. This disease was first described by Pfeiffer,[7] who pointed out its epidemic nature, its occurrence in children, its characteristics of nontender cervical glandular enlargement, the absence of tonsillitis, the slight injection of the throat, abdominal pain and enlargement of the liver and spleen. West [8] reported an epidemic of ninety-six cases limited to children, a majority of whom showed no evidence of throat infection. Tidy and Morley [9] have recently reported cases and described the disease again. They, with most other observers since Pfeiffer, have frequently noted, in addition, the enlargement of the axillary and inguinal glands but not the abdominal signs. Occasionally infection has taken place in adults, with the same important clinical features. Where a blood examination was made, lymphocytosis often was present, with moderate increase in the total number of white blood cells. Since few blood examinations have been reported, the chief features available to define this group are clinical. These features which all together present a distinct entity are: epidemicity, chief incidence in children, absence of tonsillitis, general glandular enlargement and frequent enlargement of the liver and spleen. Most observers consider the disease to be due to a specific unrecognized organism.

On the other hand, Sprunt and Evans,[10] Bloedorn and Houghton,[11] and Cross [12] and others have reported cases, the main clinical features of which have separated them from the groups just mentioned. The characteristics of these cases are: the occurrence in young adults of infection of the upper respiratory tract with systemic reaction always present, but never severe, besides the general glandular enlargement with frequent enlargement of the spleen. The cases have all shown a lymphocytosis and moderate increase in the total number of white blood cells, together wtih a blood picture which might be confused with acute leukemia. In none have hemorrhages or severe anemia been reported.

---

5. Editorial: Brit. M. J. **1**:649, 1921.

6. Morse, P. F.: Glandular Fever, J. A. M. A. **77**:1403 (Oct. 29) 1921.

7. Pfeiffer, E.: Drusenfieber Yahrb. f. Kinderh. **29**:257, 1889.

8. West: Arch. Pediat. **13**:889, 1896.

9. Tidy and Morley: Glandular Fever, Brit. M. J. **1**:452 (March 26) 1921.

10. Sprunt, T. P., and Evans, F. A.: Mononuclear Leucocytosis in Reaction to Acute Infections, Johns Hop. Hosp. Bull. **31**:357, 1920.

11. Bloedorn, W. A., and Houghton, J. E.: The Occurence of Abnormal Leukocytes in the blood in Acute Infections, Arch. Int. Med. **27**:315 (March) 1921.

12. Cross, J. G.: Conditions Simulating an Acute Leukemia (Acute Benign Leukemia), Minnesota Med., October, 1922, p. 579.

Since completion of this study, Longcope [13] has reported a series of ten cases, several of which are similar to ours. Only five patients had acute throat infection, and his Cases 1 and 2 showed no leukocytosis and only a very moderate increase in lymphoid cells. The histology of an excised lymph node in Case 2 suggested Hodgkin's disease and was unlike that in our Case 7, or that reported by Evans and Sprunt. These variations may cast some doubt as to whether his Cases 1 and 2 have sufficient clinical features to be grounds for inclusion in the group described by the last mentioned observers.

To such cases are added, in this paper, nine which were observed recently within a relatively short period of time. Their frequency suggests a much more common occurrence of the disease than is recognized at present and arouses curiosity as to its etiology. A better understanding of this type of case is desirable, not only that diagnosis and prognosis may be more certain, but that evidence may be accumulated concerning its eitology and the possible relationship to leukemia. While most of these cases, on account of their benign nature and short course, may be classified as a clinical entity and recognized without difficulty, occasional members of the group present not only clinical features but blood pictures that do not readily allow such disposal. Whether or not the cause of this disease is a specific organism is a problem concerning which no proofs are available. The usual assumption has been that such lymphatic reaction occurs with various types of infection that are usually associated with polymorphonuclear leukocytosis. The variations that have occurred in the nature of acute infections, such as influenza and encephalitis, may have a bearing on the increased frequency of the type of case here reported. Case history 1 is given in some detail. Others have been abbreviated to include only important positive findings.

REPORT OF CASES

CASE 1.—*History.*—M. J., a white man, aged 22, single, a student, entered the Students' Health Service Hospital, March 1, 1921, complaining of sore throat, fatigue and headache. He had had scarlet fever at the age of 9 years; he had also had measles, mumps and whooping cough during childhood. While stationed with the army in Texas in 1916, the patient had had a period of diarrhea and chills. He said that he had noticed slight loss of strength one month previous to entrance. On February 28, the patient first appeared at the dispensary complaining of a sore throat. The following day he returned with a temperature of 101.6 F. and was admitted to the ward, on the nose and throat service.

Phyical Examination.—On the date of admission the throat was moderately injected and on both tonsils were scattered patches of grayish white exudate. Cultures showed no predominating organism. On March 6, medical consulta-

13. Longcope, W. T.: Infectious Mononucleosis (Glandular Fever), with a Report of Ten Cases, Am. J. Med. Sc. **164**:781 (Dec.) 1922.

tion was requested. Examination showed a well developed and well nourished young man without marked prostration or anemia. The throat showed marked injection, which involved the tonsils, fauces and postpharyngeal wall. The tonsils showed a few small areas of exudate and ulceration. These later became enlarged and presented quite marked ulcerative areas. In the mucous membranes over the soft palate and anterior pillars, extending to the buccal mucosa, were several hemorrhagic areas. These persisted throughout the period of observation. The cervical lymph nodes were markedly enlarged and greater on the left, where they formed a mass from four to five cm. in diameter.

TABLE 1.—*Blood Findings in Case 1*

Date	Red Blood Cells	Hemoglobin, per Cent.	White Blood Cells	Polymorphonuclears, per Cent.	Polymorphonuclear Eosinophils, per Cent.	Polymorphonuclear Basophils, per Cent.	Lymphocytes, per Cent.	Small Lymphocytes, per Cent.	Large Lymphocytes, per Cent.	Transitionals, per Cent.	Large Mononuclears, per Cent.	Unclassified
3/ 6/21	.....	..	3,000	.....	.....	..	..	..	..	..	..	..
3/ 7/21	.....	..	4,500	13	1	..	86	..	..	..	..	..
3/ 9/21	4,672,000	95	.....	18	1	1	80	..	..	..	..	..
3/11/21	.....	..	.....	6.66	0.33	1	92	..	..	..	..	..
3/12/21	3,904,000	..	17,200	18	1	..	81	..	..	..	..	..
11/ 3/21	.....	..	7,000	50	.....	1	..	8	37	4	..	..
11/25/21	.....	..	7,900	66	1	..	..	3	23	2	4	1
2/10/22	.....	..	7,200	45	1	..	..	36	15	..	3	..
2/24/22	.....	..	7,150	55	.....	..	..	21	17	4	3	..
6/ 8/22	.....	..	.....	70	1	..	..	29	..	..	..	..

TABLE 2.—*Blood Findings in Case 2*

Date	Red Blood Cells	Hemoglobin, per Cent.	White Blood Cells	Polymorphonuclears, per Cent.	Polymorphonuclear Eosinophils, per Cent.	Polymorphonuclear basophils, per Cent.	Small Lymphocytes, per Cent.	Large Lymphocytes, per Cent.	Transitionals, per Cent.	Large Mononuclears, per Cent.
11/2/21	.....	..	14,450	19.5	..	..	9	60	10.5	1
11/3/21	6,400,000	85	16,100	21	..	..	8	67	4	..
11/7/21	4,840,000	..	15,600	....	..	..	..	..	....	..

The glands were discrete, of firm consistency and slightly tender. The axillary, epitrochlear and inguinal glands were also definitely enlarged and slightly tender. The thorax and heart were essentially negative. The spleen was definitely palpable. At this time the total leukocyte count (Table 1) was 3,000 with 86 per cent. of lymphocytes. The total leukocyte count increased to 17,200 and the lymphocyte count stayed above 80 per cent. The red cells dropped from 4,600,000 to 3,900,000 while the patient was under observation in the hospital. The temperature was irregularly intermittent and reached a maximum of 103 F. The pulse was not rapid and averaged between 70 and 80.

Prostration was moderately severe. The physical condition and fever of the patient showed no marked change up to March 13, when he was discharged. At that time the diagnostic impression was acute lymphatic leukemia. The patient, feeling perfectly well, again came under observation, Nov. 3, 1921, at the request of the physician. At that time the glands before enlarged had receded and were barely palpable. The leukocyte count was 7,000, of which 50 per cent. were polymorphonuclear leukocytes. Several examinations later, as shown in the blood chart, showed only slight increase in the relative number of lymphocytes. Seventeen months later the blood count was normal, and only a few small cervical glands were palpable.

The blood findings are given in Table 1. The urine showed a trace of albumin. The Wassermann reaction was negative and the Widal reaction atypical. One blood culture showed no growth.

CASE 2.—H. E., a white man, aged 22, single, a student, came under observation, Oct. 31, 1921, complaining of sore throat and general aching pains. The

TABLE 3.—*Blood Findings in Case 3*

Date	Red Blood Cells	Hemoglobin, per Cent.	White Blood Cells	Polymorphonuclears, per Cent.	Polymorphonuclear Eosinophils, per Cent.	Polymorphonuclear basophils, per Cent.	Lymphocytes, per Cent.	Transitionals, per Cent.	Large Mononuclears, per Cent.
3/ 6/22	.....	..	22,300	..	..	..	..	..	..
3/ 7/22	.....	..	.....	12	..	..	82	2	4
3/ 8/22	5,184,000	90	26,200	25	..	..	74	..	1
3/13/22	.....	..	16,400	31	..	..	65	2	2
3/14/22	4,532,000	90	12,800	27	..	..	66	4	3
3/15/22	.....	..	13,200	33	..	1	62	2	2
3/17/22	.....	..	12,400	..	..	..	..	..	..
3/20/22	.....	..	9,800	39	..	..	52	6	3
3/22/22	.....	85	.....	30	2	1	56	1	10
3/24/22	.....	..	8,210	32	..	..	56	7	5
3/27/22	.....	..	7,400	31	..	2	57	3	7
3/29/22	.....	80	7,800	34	..	..	48	10	8
6/ 9/22	4,992,000	85	7,000	37	1	.	57	..	5

temperature was 99.6 F. Physical examination showed moderate injection of the throat but no areas of exudate. The cervical, the axillary, epitrochlear and inguinal lymph nodes were all moderately enlarged, but not tender. The spleen was not palpable. There was slight tenderness in the right lower abdominal quadrant. The symptoms cleared up within a few days.

CASE 3.—*History.*—C. B., a white man, aged 21, single, a student, entered the Students' Health Service Hospital, March 6, 1922, complaining of sore throat and pain in the back. The onset of the present illness was noted on March 1, with sore throat and pain in the lumbar regions. The patient also complained of general aching pains and abdominal discomfort.

Physical Examination.—This revealed that there was no marked prostration. The tonsils were swollen and covered with patches of grayish-white exudate, which were confluent in some areas. The cervical lymph glands were moderately enlarged, discrete and tender. The axillary, epitrochlear and inguinal glands were likewise moderately enlarged and tender. The spleen and liver were not palpable.

Course of Disease.—On March 8, jaundice was noted, with slight tenderness along the right costal margin. On March 11, there appeared a brownish erythematous rash over the entire body, which suggested a toxic origin. On March 13, several small petechial hemorrhages were noted in the mucous membranes of the mouth. Within a day the rash over the whole surface of the body became hemorrhagic; within ten days it had largely disappeared. The temperature, which had been of an irregularly intermittent type with a maximum height of 102.4 F., reached normal within six days. The pulse rate averaged around 80.

Laboratory Findings.—The Wassermann reaction was negative. On March 15, 1922, the throat smear showed a few spirilli and fusiform bacilli. No diphtheria bacilli were found. The feces showed one test negative to guiac. One blood culture showed no growth. The patient was discharged on March 22. The blood count still showed alteration three months later, and the cervical glands were palpable.

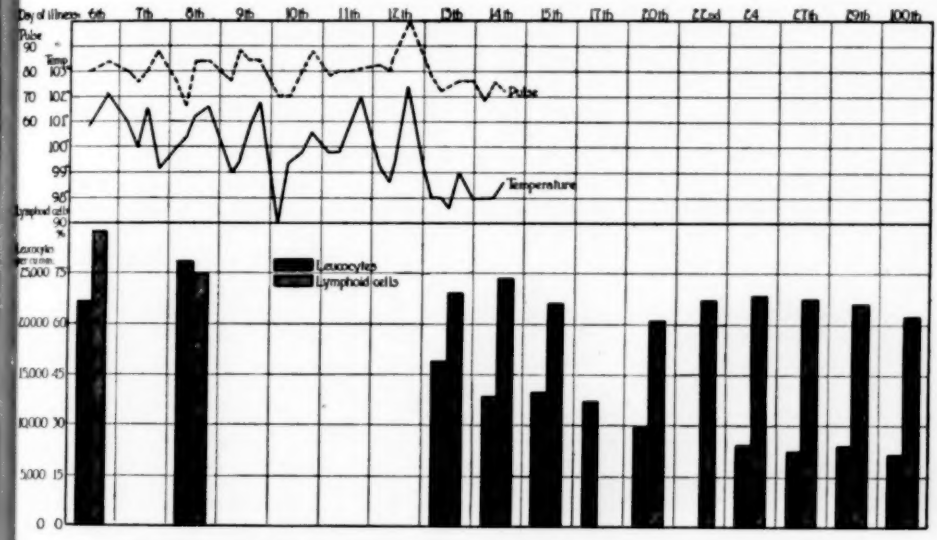


Chart 1.—Pulse, temperature, total leukocyte count and percentage of lymphoid cells in Case 3. The leukocyte count is seen to have returned to normal shortly after the fever had subsided, although there was persistence of abnormal percentage of lymphoid cells approximately three months later. The term lymphoid cell is used to describe all forms of leukocytes other than polymorphonuclear types.

CASE 4.—J. W., a white woman, aged 19, single, a student, entered the Students' Health Service Hospital, April 7, 1922, complaining of slight sore throat and malaise. The onset of the present illness was noted on April 5, with nausea and vertigo. The temperature was then normal. The following day the patient complained of headache and had fever. On the day of admission, sore throat was noted. There were a few scattered whitish patches of exudate on both tonsils, with slight peritonsillar injection. The posterior cervical group of glands, both right and left, were moderately enlarged, discrete, firm and not tender; the anterior cervical axillary and inguinal glands were

palpable but not tender; the liver and spleen were not palpable. The temperature reached a maximum of 103.2 F., and subsided on the eleventh day of illness. One blood culture showed no growth. The patient was discharged on April 17.

TABLE 4.—*Blood Findings in Case 4*

Date	Red Blood Cells	Hemoglobin, per Cent.	White Blood Cells	Polymorphonuclears, per Cent.	Lymphocytes, per Cent.	Transitionals, per Cent.	Large Mononuclears, per Cent.	Polymorphonuclear basophils, per Cent.
4/ 8/22	.....	..	15,400	20	73	4	3	..
4/10/22	4,416,000	75	26,000	18	77	1	4	..
4/11/22	.....	..	20,600	19	79	..	[illegible]	..
4/12/22	.....	..	14,400	17	77	1	[illegible]	..
4/13/22	.....	..	12,650	21	70	4	5	..
4/15/22	.....	..	12,800	19	75	1	5	..
4/19/22	.....	..	.....	28	68	[illegible]	[illegible]	..
4/26/22	.....	..	8,800	38	54	3	4	1
6/ 5/22	4,416,000	80	8,400	46	45	4	5	..

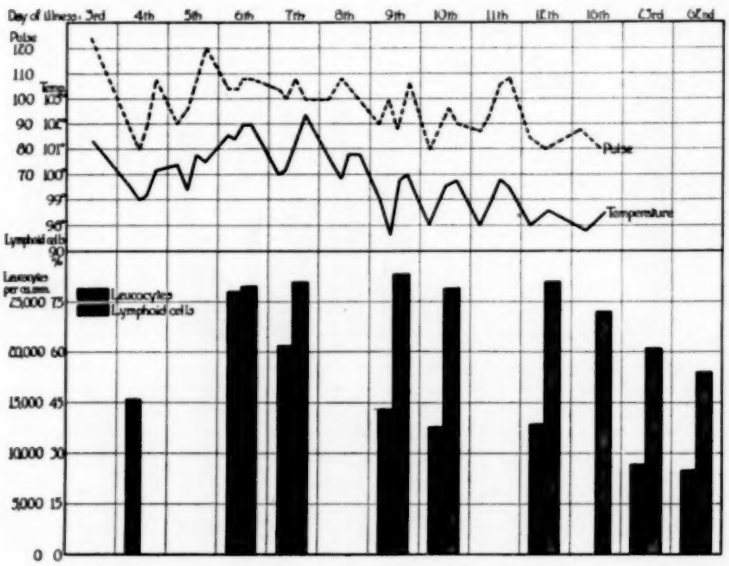


Chart 2.—Abnormal percentages of lymphoid cells in Case 4 approximately two months after recovery.

CASE 5.—A. P., a white man, aged 20, single, a student, was admitted to the Students' Health Service Hospital, May 25, 1922, complaining of sore throat. The duration of the present illness was one day. The patient had

sore throat but no other symptoms except slight malaise. Physical examination revealed moderately hypertrophied tonsils. There was a grayish white membrane over the right tonsil, and only moderate peritonsillar injection. The submaxillary glands were markedly enlarged, the left more than the right, and the other cervical glands, as well as the axillary and inguinal glands, were definitely enlarged. The spleen and liver were not palpable. The patient's temperature reached 102.2 F., and pulse rate, 96. Recovery occurred at the end of one week. Laboratory: In a throat smear taken May 27, 1921, spirilli and fusiform bacilli were present, but they were not found in abundance. The patient was discharged on June 1.

TABLE 5.—*Blood Findings in Case 5*

Date	Red Blood Cells	Hemoglobin, per Cent.	White Blood Cells	Polymorphonuclears, per Cent.	Polymorphonuclear Eosinophils, per Cent.	Lymphocytes, per Cent.	Transitionals, per Cent.	Large Mononuclears, per Cent.
5/29/22	4,224,000	80	11,000	30	2	56	6	6
5/31/22	.....	..	10,800	36	5	50	2	3
6/ 1/22	4,736,000	75	12,400	33	3	30	1	4
6/ 6/22	4,638,000	75	8,400	37	5	52	2	4
6/12/22	4,742,000	80	8,000	32	2	42	1	3

TABLE 6.—*Blood Findings in Case 6*

Date	Red Blood Cells	Hemoglobin, per Cent.	White Blood Cells	Polymorphonuclears, per Cent.	Polymorphonuclear Eosinophils, per Cent.	Polymorphonuclear basophils, per Cent.	Small Lymphocytes, per Cent.	Large Lymphocytes, per Cent.	Transitionals, per Cent.	Large Mononuclears, per Cent.
12/12/21	.....	..	6,700	38	1	..	25	24	5	7
12/15/21	.....	..	10,700	41	..	..	40	15	1	3
12/21/21	.....	..	9,200	56	1	..	19	15	4	5

CASE 6.—V. E., a white man, aged 20, single, a student, entered the Students' Health Service Hospital on December 8, complaining of headache and malaise. The present illness had its onset on Dec. 7, with sore throat, headache, malaise and a temperature of 103 F. Physical examination revealed that the throat was reddened but showed no exudate. On December 11, a rash developed, most marked over the chest and abdomen, but present also on the arms, legs and hands. It faded within one day and suggested a toxic origin. Complete recovery occurred within a week. The data are incomplete in this case but those obtained probably warrant its inclusion.

Case 7.—H. A. W., a white man, aged 36, single, a student, entered the Students' Health Service Hospital, Aug. 15, 1922, complaining of malaise, headache and stiff neck. The present illness began on Aug. 9, 1922, with the foregoing symptoms. A slight sore throat was also noted, which lasted only over night. Up to the time of entrance, the symptoms had remained about the same. Physical examination revealed palpable anterior and posterior cervical glands; those on the right side were larger, measuring 2.5 cm. The epitrochlear and inguinal glands were also palpable. All the glands were discrete, firm, and not tender. The fauces showed moderate diffuse injection. There was no exudation. The tonsils were adherent. The edge of the spleen was palpable. Table 7 contains the blood count. A roentgenogram of the chest showed no enlarged hilus glands. The urine showed a trace of albumin, no sugar and a negative sediment. Two other specimens showed no albumin.

Table 7.—*Blood Findings in Case 7*

Date	Red Blood Cells	Hemoglobin, per Cent.	White Blood Cells	Polymorphonuclears, per Cent.	Polymorphonuclear Eosinophils, per Cent.	Lymphocytes, per Cent.	Large Mononuclears, per Cent.	Transitionals, per Cent.	Unclassified
8/15/22	4,042,000	70	12,800	13	..	77	6	4	..
8/16/22	.....	..	15,600	10	1	81	3	5	..
8/17/22	.....	70	15,800	11	.	78	5	3	3
8/19/22	4,564,000	70	21,600	20	2	71	4	3	..
8/21/22	4,042,000	70	14,400	11	1	79	7	3	..
8/22/22	4,168,000	70	10,800	19	2	70	6	3	..
8/23/22	4,252,000	70	10,000	19	4	65	6	5	1

Table 8.—*Blood Findings in Case 8*

Date	White Blood Cells	Polymorphonuclears, per Cent.	Lymphocytes, per Cent.
9/26/22	15,000	43	57
10/25/22	.....	61	39

The Widal reaction in the blood was negative. One blood culture showed no growth. A cervical lymph gland was removed, a culture taken, and the gland then sectioned. The culture showed no growth. Microscopic examination showed simple hyperplasia of the type noted in nonsuppurative adenitis. The maximum temperature of 101 F. was noted on day of admission. Patient had recovered two weeks after onset. At that time the lymph nodes noted before were still palpable. The patient was discharged on August 24.

Case 8.—E. T., a man, aged 21, single, a student, came under observation on Sept. 26, 1922, complaining of sore throat and malaise. During the last two months the patient had had frequent sore throats. During the previous week this symptom had been worse and had been accompanied by marked malaise and exhaustion. Physical examination showed throat injection without tonsillar exudate. The interior and posterior cervical, axillary, epitrochlear and inguinal lymph glands were moderately enlarged, but not tender. The spleen was palpable. The temperature was 99.6 F. The symptoms subsided within two weeks. When the patient was seen one month later, the lymph nodes, but not the spleen, were still palpable.

CASE 9.—C. H., a white man, aged 19, single, a student, entered the Students' Health Service Hospital, Oct. 30, 1922, complaining of sore throat and stiffness and swelling of neck. The onset of the present illness occurred, Oct. 19, with swelling of the right side of the neck. Four days later the

TABLE 9.—*Blood Findings in Case 9*

Date	Red Blood Cells	Hemoglobin, per Cent.	White Blood Cells	Polymorphonuclears, per Cent.	Polymorphonuclear Eosinophils, per Cent.	Polymorphonuclear basophils, per Cent.	Small Lymphocytes, per Cent.	Large Lymphocytes, per Cent.	Transitionals, per Cent.	Large Mononuclears, per Cent.	Unclassified
10/30/22	.....	85	11,750	56	..	...	23	13	5	3	...
11/ 1/22	4,350,000	..	.....	42.5	..	...	40.5	4.5	10	..	2.5
11/ 2/22	....	..	6,150	32	..	...	58.5	2.5	5	2	...
11/ 3/22	.....	..	.....	30	..	...	40	23	5	2	...
11/ 4/22	... .	..	.....	37	..	1.5	55.5	2	1.5	..	2.5
11/ 7/22	.....	..	5,850	42	..	...	46	6	4	..	2
11/ 9/22	.....	..	9,800	54	0.5	1	35	7.5	1	..	1
11/15/22	.....	..	.....	78	.	...	12	2	3	..	5

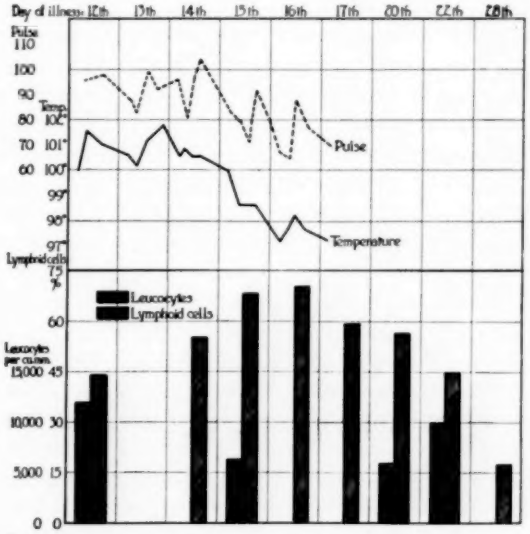


Chart 3.—This shows that in Case 9 the maximum percentage of lymphoid cells was reached as the temperature became normal; also the comparatively rapid return of percentage of lymphoid cells to normal.

throat became slightly sore with stiffness of the neck. On being examined on Oct. 31, the patient showed no prostration. Both tonsils showed ulcerated areas with only moderate surrounding injection or edema. Anterior and

posterior cervical glands were enlarged, especially the group beneath the sternocleidomastoid muscle, which bulged distinctly in its upper third. The glands were only slightly tender. The surrounding tissues were not inflamed. The axillary and inguinal glands were moderately enlarged, the epitrochlears slightly so. The spleen was readily palpable. Diagnostic impression from clinical findings was acute glandular infection with lymphocytosis. Throat smears gave no predominating organisms. One blood culture was negative. The temperature reached a maximum of 101.8 F., and became normal four days after admission. The throat cleared up during this period. Total duration from the time of the first symptom to the date of normal temperature was fourteen days. The patient was discharged on December 4. He was again seen Nov. 9, 1922, when the glands were smaller and the spleen had definitely receded, although it was still palpable. On December 20, the spleen was not palpable.

COMMENT

The foregoing patients, eight males and one female, were all young adults. No predisposing factors were present. In all the cases, there was systemic reaction; and the onset was associated with malaise, sore throat and fever. In Case 9, swelling of the neck occurred four days before the throat became sore. In two persons prostration was moderately severe; in the others the course of the disease was mild. Sore throat was the chief complaint through the course of the disease. In five cases, scattered patches of exudate were present on both tonsils. In Case 1, there were also definite ulcerated areas over the tonsils, marked edema and injection of the fauces, with hemorrhages in the buccal mucosae later, and in Cases 3, 5 and 9 also marked inflammatory reaction. The patient in Case 3 developed a purpuric rash, the occurrence of which is of interest in view of the hemorrhages in the mucous membrances and skin common in leukemia. In all other cases, the throat showed only injection without exudation or ulceration. The superficial lymph glands, especially the group in the superior triangle of the neck extending under the sternocleidomastoid muscle, were enlarged (from 2 to 3 cm.), the increase being symmetrical in the majority of cases; they were discrete, firm and occasionally slightly tender. The axillary, epitrochlear and inguinal glands were likewise enlarged but rarely tender. In Case 3, while the cervical glands did not show as much enlargement as is mentioned in the foregoing, those in the inguinal region were even greater in size. The periglandular tissue did not show edema, and the marked tenderness sometimes present in acute cervical adenitis was also absent. In all the patients under observation, the glandular enlargement was definite and above the limits seen in normal persons. The spleen was palpable in four persons, the liver in none. In one case a transient jaundice developed. Blood cultures taken in five cases showed no growth.

The blood count in Case 1 showed the greatest variation, there being first a leukopenia with 3,000 white cells, followed by an increase

within six days to 17,200 cells, 81 per cent. of which were lymphocytes. As high as 92 per cent. of lymphocytes were recorded; therefore an absolute lymphocytosis was present. In the other cases leukocytosis was always present, the maximum counts varying from 10,700 to 26,200; in six cases 15,000 or above. The total percentage of lymphocytes varied from 57 to 92. In all cases, the total leukocyte count approached normal as the defervescence occurred. It is of interest that Cases 1 and 3, with comparatively greater systemic reaction, including the hemorrhages before described, still showed, eight and three months later, respectively, increased percentages of lymphocytes; also that in Cases 1, 3, 4 and 7, with delay in return of lymphocyte percentages to normal, there was persistence of glandular enlargement, although lessened in degree. On the other hand, Cases 5, 6, 8 and 9, with a milder reaction, showed, from fourteen to thirty days after the onset of the illness, a return to approximately the normal percentage of lymphocytes. In Case 9, during a four-day period of defervescence, there was a steady increase in percentage of lymphocytes. One week thereafter, however, 54 per cent. of polymorphonuclear leukocytes was reached. Anemia of any marked degree was not observed.

In another series of nine cases with acute throat infections, taken without selection, in which there was no general lymphadenosis and enlargement of the spleen, total leukocyte counts have varied from 11,500 to 17,100, and the polymorphonuclear leukocytes from 74.5 to 89 per cent. This control series in a similar group of young adults has been included to show the dissimilarity between the characteristics of the group of cases here described and of acute tonsillitis and pharyngitis unassociated with the enlargement of lymph glands and spleen.

Although there was considerable variation in the clinical pictures presented, there were certain constant features in all the cases under observation which apparently define a clinical entity. Early in the course of the disease, the tonsils or pharynx, in all cases, showed acute infection as evidenced by areas of exudate and ulceration or by injection alone. This common and early presence of tonsillar and pharyngeal infection commands attention as the most likely portal of entry. The cervical adenopathy was noted first and was most pronounced, as best illustrated in Case 5. In Cases 2 and 8, systemic reaction and pyrexia, although minimal, were definitely associated with acute throat infection. The comparatively low total leukocyte count is of course unusual in leukemia, but is not itself a differentiating sign in the early stages. Hemorrhage into the mucous membranes and skin was observed in two cases, and differed only in its moderate degree from that seen in the leukemia. The anginal throat similar to that of leukemia has likewise been observed

in two cases. Organisms of Vincent's angina were found in the throats in four cases, the smears, however, showing no marked preponderance of such forms. The throats, with their well developed inflammatory reaction, did not have the appearance characteristic of Vincent's angina. The systemic reaction, also, was out of proportion to that seen in Vincent's angina. In addition, the blood picture in observed cases of true Vincent's angina has never shown marked or constant alteration in percentage of lymphocytes. In view of the presence of the fusiform bacilli and spirilli in diphtheria and other throat infections, apparently little significance can be attached thereto in the cases here observed. The fastigium never extended over three weeks and averaged approximately eleven days. The fever reached a maximum of 103 F., was an irregular, intermittent type, and fell by lysis. The pulse rate increased with the temperature. The patients are all well at present, seventeen months having elapsed since they first came under observation.

The hemorrhagic tendency evidenced in two cases suggests a similarity to leukemia. However, these hemorrhages in the mucosa and skin have not been extensive and have not been associated with anemia. The lymphocytosis of chronic focal infection does not suggest itself in any case.

It is highly important that the benign nature of these cases be recognized and favorable prognosis given. From the standpoint of etiology, emphasis on the resemblance to leukemia should broaden the scope of study.

Dr. Downey's study of blood morphology indicates characteristics which separate this group in a similar manner from other pathological conditions associated with lymphocytosis. When taken with the constant clinical characteristics described, a distinct disease entity is apparently defined. From blood findings, prediction of clinical features has been possible, and from clinical features the blood findings. The clinical features of Case 9 were typical and suggested the blood changes afterward reported by Dr. Downey. Such features are readily recognized, and always indicate that blood examination is necessary. The usual cases of tonsillitis and pharyngitis have not shown these features and have always been associated with polymorphonuclear leukocytosis.

SUMMARY OF CLINICAL STUDY

Certain constant features found in the cases described are: (1) the occurrence in young adults of an acute tonsillitis or pharyngitis with systemic reaction; (2) absence of anemia; (3) enlargement of lymphatic glands and frequently of the spleen; (4) lymphocytosis; and (5) the comparatively rapid recovery of the patient.

These features differentiate the group studied from severe infections in which anemia and lymphocytosis have often led to confusion with leukemia. From glandular fever, with its highly epidemic nature, its occurrence in children, and its absence of tonsillitis or marked pharyngitis, differentiation is also clear.

Although many of the symptoms and signs of acute leukemia are present in this group of cases, their moderation, together with the absence of anemia, defines a condition quite dissimilar. None of the cases observed have shown either the progressively malignant course with prostration and anemia, which is usually present in acute leukemia, or the high leukocyte counts, which are also usually present.

These cases, as has been shown, present a distinct clinical entity. In the absence of knowledge of the etiology of the disease, the descriptive term acute lymphadenosis with lymphocytosis is suggested.

PART II. HEMATOLOGIC STUDIES*

HAL DOWNEY, PH.D.

The group of cases described by Dr. McKinlay is of special interest to the hematologist: first, because it adds another group to the long list of reported cases of infectious disease accompanied by lymphocytosis instead of the usual polymorphonuclear reaction; and second, because numerous authors have had difficulty in distinguishing between the blood picture of such conditions and that of cases of acute leukemia. Prognosis was uncertain in cases reported by some authors, and the diagnosis of acute leukemia has been made by others in cases in which the complete recovery of the patient proved the error. In one of our own cases, the outcome was somewhat in doubt, in spite of the negative blood findings, because the clinical symptoms were similar to those of acute leukemia. In another one of our cases (Case 3), the blood showed some leukemic features, but the clinical findings, with some features of the blood to be mentioned later, would not support a diagnosis of leukemia.

REVIEW OF THE LITERATURE

Since in only one of the cases of this group (Case 3) and of many other cases of nonleukemic lymphocytosis with other types of infection which have been observed by the writer, were there any blood features

---

*From the Hematological Laboratory, Department of Animal Biology, University of Minnesota. Aided by a grant from the Research Funds of the Graduate School.

suggesting leukemia, it would seem that much of the difficulty in diagnosis has been due to inadequate study of the blood. Perusal of the literature shows this to be the case. With a few notable exceptions, the papers dealing with the subject show little evidence of detailed blood studies. Much attention is given to total counts, percentages, etc., but little to detailed cytology. In most cases, there are no illustrations accompanying the papers, so that it is impossible to pass judgment on the cells described. Lymphoblasts, immature lymphocytes, etc., are mentioned, but often it is impossible to determine the type of cell the authors have in mind when they are thus described. Thus, when it is stated that the blood picture resembled or was identical with that of acute leukemia, the statement must be accepted with some reservation, unless accompanied by descriptive or illustrative proof. Such proof is furnished in the papers of Sprunt and Evans [10] and of Bloedorn and Houghton,[11] and it is evident from their figures and descriptions that there is no danger of confusing the blood picture of such cases with that of acute leukemia.

That a temporary leukemic blood picture, both myelogenous and lymphatic, may accompany infectious diseases of various types is a well known fact (Türk,[14] Naegeli,[1] Roth,[15] Stursberg,[16] Klienenberger,[17] A. Herz,[2], F. Marchand,[18] and many others), and a blood picture which leans more or less toward leukemia has been produced experimentally by Lüdke [19] and Pappenheim.[20]

Organ changes more or less similar to those of leukemia, particularly myelogenous leukemia, are known to occur with infectious dis-

---

14. Türk, W.: Klinische Beobachtungen über das Verhalten des Blutes bei akuten Infektionskrankheiten. (Cited from A. Herz) Braumüller, Vienna and Leipzig, 1898. Septische Erkrankungen bei Verkümmerung des Granulocytensystems. Wiener klin. Wchnschr., 1907, No. 6. Vorlesungen über klinische Haematologie. Wien. u. Leipzig, Braumüller, 1912.

15. Roth, C.: Ueber einen bemerkenswerten Blutbefund bei einem Fall von subakuter Miliartuberkulose. (Ein Beitrag zur Frage der akuten myeloischen Leukämie), Ztschr. f. klin. Med., vol. 78, 1913.

16. Stursberg, H.: Zur Differentialdiagnose zwischen akuter Leukämie u. Sepsis, mit besonderer Berücksichtigung der "Sepsis bei Verkümmerung des Granulocytensystems," Med. Klin. **8**:520, 1912.

17. Klienenberger: Das Blutbild der akuten Leukämie als passageres Symptom, München. med. Wchnschr. **61**:1159, 1914.

18. Marchand, F.: Ueber ungewöhnlich starke Lymphocytose im Anschluss an Infektionen, Deutsch. Arch. f. klin. Med., 1913, vol. 110.

19. Lüdke, H.: Die experimentelle Erzeugung leukämischer Blutbilder, Verh. d. deutsch. Kongr. f. innere Med., 27ster Kongr., Wiesbaden, 1910.

20. Pappenheim, A.: Atlas der menschlichen Blutzellen, Jena, G. Fischer, 1905, 1912. Grundriss der hämatologischen Diagnostik und praktischen Blutuntersuchung, Leipzig, Werner Klinkhardt, 1911. Die Zellen der leukämischen Myelose, Jena. G. Fischer, 1914. Haematologische Bestimmungstafeln, Leipzig, Werner Klinkhardt, 1920.

eases, and they have been produced experimentally in various ways by Dominici,[21] Werzberg,[22] Hertz,[23] Isaac and Möckel.[24]

Many authors have discussed the intimate relation between acute leukemia and sepsis, and Sternberg [25] claims that acute leukemia is an infectious disease. This view is supported to some extent by Türk, who believes that there is some relationship between what he calls "lymphatic reaction" and lymphatic leukemia. A. Herz, basing his opinion on cases of his own and of Türk, concludes that there are cases of general infection in which the blood pictures are identical with those of acute leukemia, both myelogenous and lymphatic, and that the only difference between the two is in the final outcome. He adds that if acute leukemia is an infectious disease, we may assume the existence of a curable form.

Blood pictures which are more or less leukemic in form have also been noted in cases similar to the group reported here. Three of Türk's cases seem to be closely related. They were cases of angina and general infection accompanied by slight swelling of lymph nodes and moderate enlargement of the spleen. The blood picture is described in detail for one of the cases. There were 17,000 leukocytes, with 16 per cent. granulocytes. The other cells were partly normal lymphocytes, but mostly atypical, unripe lymphocyte forms.

Naegeli has also had experience with cases similar to those of our group. On page 472, he points out the difficulties in distinguishing between lymphatic leukemia, lymphocytosis and "lymphatic reaction." Severe leukopenia of 800 to 2,000 white cells most of which are lymphocytes is likely to be sepsis with exhaustion or destruction of the marrow. "Lymphatic reaction" causes the greatest difficulty, because the blood shows not only high relative and absolute lymphocyte values, but also atypical lymphocytes and lymphoblasts. But these are usually cases of acute infection with fever, which are soon cured,

---

21. Dominici, H.: Sur l'histologie de la rate a l'état normal et pathologique, Arch. de méd. expér. et d'anat. pathol. **13,** 1901. Etudes sur le tissu conjonctif et les organes hématopoiétiques des mammifères, Arch. d'Anat. Microscop **17,** 1921.

22. Werzberg, A.: Neue experimentelle Beiträge zur Frage der myeloiden Metaplasie, Virchows Arch. f. path. Anat. **204**:272, 1911.

23. Hertz, R.: Zur Frage der experimentellen myeloischen Milz-Metaplasie, Ztschr. f. klin. Med. **71,** 1910.

24. Isaac, S., and Möckel, K.: Ueber experimentelle schwere Anämien durch Saponinsubstanzen, Verh. d. deutsch. Kongr. f. innere Med., 27ster Kongr., Wiesbaden, 1910, p. 471.

25. Sternberg, C.: Primärerkrankungen des lymphatischen und hämatopoetischen Apparates; normale und pathologische Morphologie des Blutes, Ergeb. d. allgem. Path. u. path. Anat. (Lubarsch-Oster tag), 1905. Ueber die Rolle der Lymphozyten bei den chronischen infektiösen Entzündungen, Verh. d. deutsch. path. Gesellsch. 16 Tagung, Marburg, 1913.

with the blood gradually returning to normal. "For a certain time the diagnosis may be impossible." This condition may be further complicated by a clinical picture which is similar to acute leukemia and is marked by fever, enlarged glands and spleen, and prostration. On pages 485 and 486, Naegeli describes several of his own cases and several from the literature which are similar to those of our group. In many of his cases, he found large pathologic lymphocytes having a blue staining cytoplasm which reminds one strongly of plasma cells; and on account of these cells Naegeli was able to decide against leukemia in two of the cases. He has also noted a somewhat similar blood picture in abdominal typhus, and observed a high lymphocytosis with immature cells in fetal syphilis, which might be diagnosed as myeloblastic leukemia.

Cabot's [3] Cases 3 and 4 seem to be similar to those of our group. The blood contained 71 per cent. and 75 per cent. lymphocytes, but from the description of the cells it is evident that the blood picture is not leukemic. Nevertheless, Cabot seems to think that there is danger of confusing the picture with leukemia, for he states: "The distinction between such a lymphocytosis (accompanying a widespread adenitis) and leukemia depends upon the recognition of an infectious origin for the adenitis, upon the lesser degree of lymphocytosis in the infectious type, and upon the course of the disease."

Other writers see leukemic features in the blood pictures of the cases which they report, although there is nothing about the morphology of the cells to warrant such a conclusion. Thus Sanders [4] reports a case of fatal Ludwig's angina in which the blood contained numerous large cells having the morphologic characters of lymphocytes. The leukocyte counts ran from 11,000 to 23,000 with 96 per cent. lymphocytes, mostly of the larger variety. The smears contained cells showing all gradations from small lymphocytes to the large cells having the morphology of lymphocytes. In spite of these morphologic characters, Sanders seems to think that he has a blood picture of acute myeloblastic leukemia, for he states: "It seemed impossible to conceive that lymphocytes could migrate into the cellular tissues of the floor of the mouth and neck in sufficient numbers to account for the extensive board like swelling. We therefore believe that they are the immature histological antecedents of the granular myelocyte; viz., the nongranular myeloblast, and that future studies by the more recent methods will show the leukocytes of the infective lymphocytoses, and most likely the acute lymphoid leukemias to be of myeloid instead of lymphoid origin."

Bloedorn and Houghton [2] describe four cases in young adults which are similar to those of our group. The blood picture was

essentially the same in all four cases. The characteristic cells as described and figured seem to be the same as those of one of our types (Type II, Fig. 7), but they are described as "lymphoblasts." The authors recognize certain minor differences between the blood in their cases and acute leukemia, but, nevertheless, they seem to be impressed with the difficulty of making a diagnosis, for they state: "The differentiation of this type of case from acute lymphatic leukemia may be particularly difficult. The absence of degenerated and fragile cells in the blood smears, the early return of the temperature to normal, the mild course, the absence of hemorrhagic spots and the absence of particularly high leukocyte counts are distinguishing features." None of the cells shown in their figures have any resemblance to the primitive stem cells which are invariably present in acute lekemia. They seem to think that the low total leukocyte counts would distinguish the cases from leukemia, a statement which is hardly in accord with the facts.

Morse,[26] in reporting two cases of "glandular fever" in adults, describes the characteristic cells as "lymphoblasts," but he recognizes the fact that the blood smear is quite different from that of leukemia.

Sprunt and Evans [1] have made a complete blood study on a group of six cases of adults which are identical with those of our group. Their paper is illustrated with a good colored plate, from which, and the unusually complete descriptions, it is evident that the blood picture is in no way related to that of acute leukemia. They believe, however, that differentiation from beginning lymphatic leukemia may be difficult, especially from the clinical side.

Longcope [13] has recently reported a series of ten cases of "infectious mononucleosis," most of which are similar to the cases of our group. The importance of the atypical mononuclear lymphoid cells is realized and they are described in some detail, but there are no illustrations. They are evidently identical with the cells seen in our own cases. Because they do not respond to the oxydase reaction, Longcope believes that they are derived from true lymphoid tissue. He also notes that these cells show no relations to the large mononuclears of normal blood, which corresponds to the findings in our own group of cases.

Longcope recognizes the distinction between these cases and leukemia. After pointing out that they are in no way related to tuberculosis, typhoid fever, Hodgkin's disease and syphilis, he states: "The resemblance to leukemia is perhaps most striking, but the early and marked enlargement of the lymph nodes, the absence of anemia and of purpura, and the histological and biological characteristics of

26. Morse, P. F.: Glandular Fever, J. A. M. A. **77**:1403 (Oct. 29) 1921.

the abnormal mononuclear elements of the blood practically exclude the possibility of considering these cases as instances of mild and transient acute leukemia."

The foregoing outline of certain phases of the literature should be sufficient to indicate the importance of further study of cases of lymphocytosis, particularly of cases accompanied by general adenopathy, like those of our own group, in which the diagnosis has often been uncertain until made clear by the progress of the case. More attention should be given to cytologic studies of the blood with special reference to possible relationships with the leukemic blood picture. It is with the hope of contributing somewhat to this as well as to the clinical side of the question that we are reporting another group of these cases.

AUTHOR'S CASES

Among the cases which have come under our observation, three types can be recognized hematologically. These differences are in no way related to leukocyte counts and percentages, but depend solely on the morphologic features of the cells which give the blood its characteristic picture. There is nothing in the clinical findings to warrant such a subdivision of the group, so they are probably of little practical importance, although Type III (Case 3, Figs. 8 to 11), which shows some leukemic features, might cause some difficulty in diagnosis, especially if cases occur in which these features are more pronounced than they were in our one case of this type. Each case shows minor variations indicating gradations between the types. This shows that the division of the cases into three types is entirely artificial; nevertheless, it serves to indicate the great difference in the character of the blood picture in the various cases of the group.

Our Type I (Cases 1, 5 and 8, Figs. 1 to 6) seems to be the common type, for five of our own cases were of this type, as were also the six cases reported by Sprunt and Evans, some of Naegeli's cases and the four cases of Bloedorn and Houghton. The indistinct halftone figures accompanying the paper of the latter authors are of cells which look more like the cells of our Type II (Fig. 7), but according to the description given, the cells are more like those of our Type I. The colored plate published by Sprunt and Evans shows that their cases were identical with our Case 1. Their cells 3, 4, 5 and 7 look as though they had been taken from our case.

These authors state that the blood picture in the five cases observed from the beginning was the same, showing practically no variations. Bloedorn and Houghton also noted little variation in the blood picture of their four cases. Naegeli's cases showed considerable variation in

the blood picture; some were of the leukemic type, while others clearly belong to our Type I (Figs. 1 to 6).

Our Case 1 will be described in some detail, because this case showed many of the clinical features of acute leukemia and was so diagnosed in spite of the negative blood findings. The negative blood report was based on the morphology of the cells and not on the counts. The first leukocyte count on March 6, 1921, gave a total of 3,000 with 83 per cent. lymphocytes. Five days later, the total count had gone up to 17,000 with 92 per cent. lymphocytes. Such counts are common in acute leukemia, and are practically identical with the counts obtained in a case of acute lymphatic leukemia which we have illustrated with Figures 12, 13 and 14 of our plate in order to compare the cytology of acute leukemia with that of benign lymphocytosis.

Typical cells from our Case 1 are illustrated in Figures 1 to 6. They are not excessively large cells, as can be seen by comparison with the other figures of the plate which are all drawn to scale by outlining with the camera lucida at the same magnification. When compared with the lymphoid cells of normal blood, it is seen that they are all atypical, pathologic forms, including even the medium-sized lymphocyte of Figure 4, which has a more basophilic and vacuolated cytoplasm than is usual for these cells.

Nearly all of the lymphoid cells of this blood when first examined were atypical to the extent illustrated in the figures. In spite of the marked lobulation of the nuclei of many of the cells, which is quite characteristic for this particular case, it is evident that all of the cells belong to the lymphocyte series, for it is possible to select a complete series of transition stages leading from a lymphocyte like the one shown in Figure 4 to the large cells of Figures 1, 2, 3 and 5.

In building up a series of this kind, particular attention must be given to the inner nuclear structure. The size and form of the nucleus are of little value in determining genetic relationships or stage of differentiation of the cells, but the quantity and distribution of chromatin and its relation to the parachromatin is of great importance. This is a principle which has been emphasized time and again by Pappenheim and which is now universally recognized by hematologists who are working on the pathologic side of blood. Pappenheim believes that the form of the nucleus and its relative size determine the age of the cell at any particular stage of differentiation.

According to this scheme, a wide-bodied cell having a nucleus with inner structure similar to that of Figure 13, but lobulated like those of Figures 1, 2 or 5 would be an older, "leukocytoid" lymphoidocyte (myeloblast of Naegeli), while cells having the inner nuclear structure of lymphocytes, but with lobulated nuclei surrounded by a wide cell

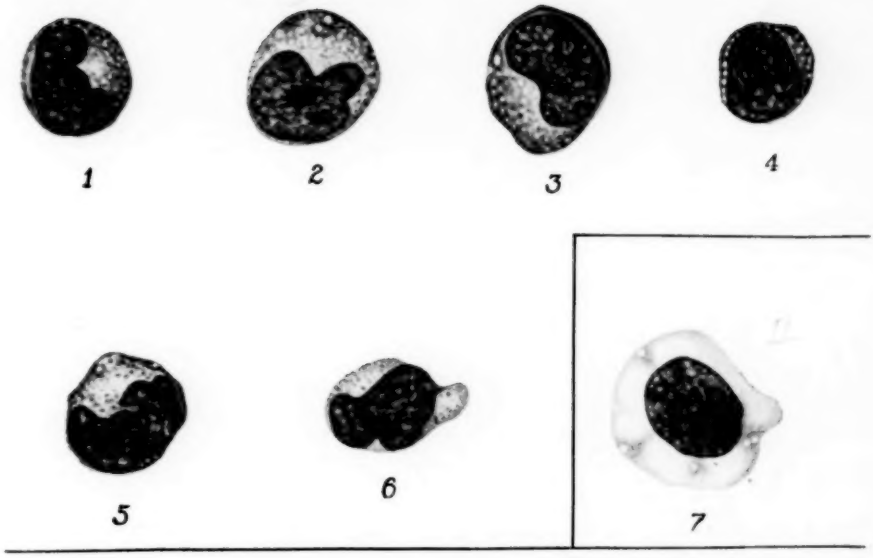
body would be older, leukocytoid lymphocytes. In other words, it is quite possible to distinguish between morphologic characters which are due to immaturity and lack of differentiation and those which are due to the process of "aging" and further differentiation.

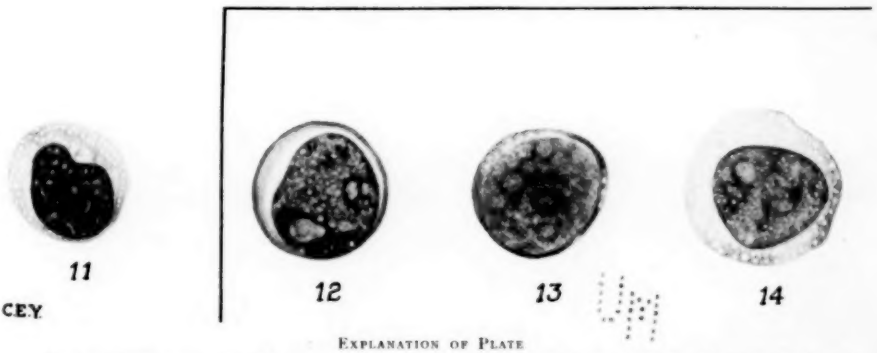
Perusal of the literature on lymphocytosis shows that these principles must be kept more clearly in mind when studying this condition, and especially when it is desired to compare it with true leukemia. We find that the terms "lymphoblast," "germ center cell," "immature cell," etc., have been used in cases that did not justify such terminology, and this is undoubtedly partly responsible for the prevailing opinion that it is difficult to distinguish hematologically between these cases of benign lymphocytosis and acute leukemia. That there may be real difficulty in some cases has already been admitted, but this is certainly not true of the average case, as we hope to show by this report.

Applying these principles to the cells of our Case 1, it is readily seen that the characteristic cells are highly differentiated, mature, "leukocytoid" lymphocytes, rather than immature "lymphoblasts." The lymphocyte type of nucleus is seen in all of them, although it may be slightly modified in the largest cells (Figs. 2 and 3), which have probably been derived from large "mesolymphocytes."

Figures 4 and 5 are best for the characteristic structure of the lymphocyte nucleus. The chromatin forms a coarse network of heavy strands and masses which are not sharply separated from the parachromatin. This gives the nucleus a cloudy appearance which is quite characteristic for the lymphocyte. In some cells there is a slight condensation of the chromatin with corresponding separation from the parachromatin, resulting in the formation of a more definite network (Fig. 1). The dense rounded or angular blocks of chromatin characteristic of the nuclei of plasma cells, of which there are a few in this blood, are the result of further condensation. The plasma cell nuclei are somewhat similar to the nucleus of Figure 7, which is from another case.

In some of the larger cells, there may be a slight tendency toward a more diffuse arrangement of the chromatin (Fig. 2), but this is never sufficient to warrant classification of the cell as a lymphoblast or particularly immature cell, because the lymphocytic nature of the nucleus always remains evident. The difference is immediately apparent if Figure 2 is compared with the immature lymphocytes of a case of acute lymphatic leukemia shown in Figures 12, 13 and 14. Figure 13 is the most immature cell of this series, and it is identical with the "myeloblast" of Naegeli. It is followed by the older cells shown in Figures 14 and 12, which illustrate the gradual differentiation of the lymphocyte from the "stem-cell." These cells are characterized by the





CEY

EXPLANATION OF PLATE

All the figures are drawn with the same magnification (Zeiss 2 mm. apochromatic objective, N. A. 1.4 and compensating ocular 8) and outlined with the camera lucida, drawing board at the height of the stage.

Figs. 1-6.—The predominating types of lymphoid cells in Case 1. The clinical picture of this case was almost similar to that of acute leukemia, but the blood contained no immature cells. The predominating cells of Cases 5, 6, 8 and 9 were almost similar to these. They and Case 1 are grouped as Type I.

Fig. 7.—The characteristic cell of Type II, which includes Cases 2, 4 and 7, and one case reported by Dr. Cross. The nuclei of these cells frequently resemble those of plasma cells derived from lymphocytes. The cytoplasm is not so basophilic and not so vacuolated as in Type I.

Figs. 8-11.—Cells from Type III, Case 3. In general, the cells from this case resemble those of Type I, but some of them show leukemic features, such as the azurophil rod in the large vacuole of Figure 11, narrow-bodied cells with indented nuclei (not illustrated), and cells with nuclei which are more or less immature, i. e., with diffuse sievelike arrangement of chromatin and nucleoli (Figs. 8 and 9).

Figs. 12-14.—Immature cells from a case of acute lymphatic leukemia. These are included in order to facilitate comparison of benign lymphocytosis with acute lymphatic leukemia. The total count and lymphocyte percentage in this case were similar to the counts in Case 1 (Figs. 1 to 6).

extremely fine and regular chromatin network, the presence of nucleoli, and the abundant and distinct parachromatin which seems to be composed of innumerable fine, rounded granules embedded in a continuous mass of chromatin. This "leptochromatic" structure is seen best in cell 13, while cells 14 and 12 show how the nuclear structure gradually becomes coarser ("pachychromatic"—Pappenheim) with progressive differentiation.

The three cells just referred to show all of the morphologic signs of immaturity and lack of differentiation, while the cells of our Case 1 (Figs. 1 to 6) are highly differentiated, mature and functionally active cells. Their state of differentiation is read from the inner structure of the nucleus, indicating mature lymphocytes in this case, while the age of the cells and their functional activity are expressed by the lobulation of the nucleus, the vacuolization of the cytoplasm, the large amount of hyaloplasm and the azure granules. Signs of aging and functional activity may also be seen in immature cells, such as the one illustrated in Figure 14, which is a cell having a nucleus close to that of the stem-cell, but with a wide cell body.

The foregoing is the explanation which Pappenheim [17] gives for the varying morphology of the lymphoid cells. It may or may not be the complete explanation of the underlying causes of morphologic variability of the cells, but nevertheless it serves the purpose of enabling us to draw a sharp line between cytologic characters due to immaturity and those which are due to some other cause. There were no immature cells in our Case 1.

The nuclei of the larger cells are frequently placed eccentrically and are generally lobulated or indented, as shown in the illustrations. Many of the smaller cells also have irregular nuclei (Fig. 6). There is an occasional cell with a very wide and pale cell body consisting mostly of hyaloplasm, but with the nucleus of a mesolymphocyte. A few of the larger types of cells have nuclei which nearly fill the cell, and these large nuclei may be irregular in outline.

The cytoplasm in the predominating type of cell of all of the cases of Type I is quite characteristic. The degree of basophilia varies somewhat, but most of the cells are very basophilic, much more so than is usual in the normal large lymphocyte or large mononuclear. There is an occasional cell with the nuclear and cytoplasmic characters of a plasma cell, but most of them do not have the nuclear structure of plasma cells, although their spongioplasm may be just as basophilic. With Wright's stain the spongioplasm appears as dark blue or slate blue, finely granular or flaky, material with a pale yellowish background of hyaloplasm. Its distribution is such that it gives the cytoplasm a vacuolated, foamy or mottled appearance. The peripheral

portion of the cell may contain relatively more spongioplasm and therefore appear darker and more homogeneous than other parts of the cytoplasm. If the nucleus is indented, as is frequently the case, the cytoplasm in the neighborhood of the indentation contains relatively more of the yellowish hyaloplasm and is, therefore, lighter than the rest of the cell.

Frequently (Case 1) there are one or more azurophil granules embedded in the hyaloplasm of this region, which give the whole structure the appearance of a centrosphere. Most of the atypical cells contain azurophil granules, and they are quite abundant in most of the larger cells. They are usually of the lymphocytic type, i. e., fine and carmin red. There are a few cells with large spherical granules. Variations were noted in the number and size of the azure granules and in the number of cells containing the granulation in the different cases of Type I. These will be referred to more specifically in the notes on these cases.

The blood picture of Case 1 returned slowly to normal, although the patient was clinically well three months after the onset of the disease. After eight months, the total number of leukocytes was normal, but 50 per cent. of them were lymphocytes with a few of the atypical forms. Eleven months after the beginning of the illness, the atypical cells had disappeared, but the differential count still showed 50 per cent lymphocytes with a normal total leukocyte count.

In order to avoid needless repetition, the other cases of Type I (Cases 5, 6, 8 and 9) will be described in the form of brief notes comparing the cases with Case 1.

TYPE I CASES

CASE 5.—The atypical cells are not so basophilic and there are not so many with lobulated nuclei as in Case 1, although cells with eccentric nuclei are quite numerous. Their nuclear structure shows that they are modified lymphocytes. A few of them contain nucleoli, but these are surrounded by heavy masses of chromatin, so that the nucleus still preserves its lymphocytic character. There are no other signs of nuclear immaturity. The cytoplasm is spongy and vacuolated and it rarely contains azure granules. There are a few basophilic monocytes with greatly lobulated nuclei and cytoplasm loaded with fine azurophil granules. These may be mistaken for neutrophilic myelocytes if the cytologic analysis is not made with sufficient care. Similar cells were not seen in Case 1. Most of the atypical cells had disappeared eight days after the first examination.

CASE 6.—Large and medium-sized atypical lymphocytes similar to those of Case 1 are present, but there are not so many large cells, the lobulation of the nucleus is not so extreme, the cell-body is not so wide, and the azure granulation is rather coarse. Cytoplasmic vacuoles are present and the spongioplasm is basophilic. There are many more normal small and medium-sized lymphocytes than in Case 1. A small percentage of neutrophilic metamyelocytes was noted.

CASE 8.—The atypical cells are similar to those of Case 1, except that the nuclei are not so lobulated. Azure granules are present in most of the cells, including the very basophilic ones. This case contains more cells of the monocyte type with lighter, lobulated nuclei and abundant fine azure granulation in the cytoplasm. The nuclei of these cells do not show the coarse chromatin strands seen in the lymphocytic type of cell (the atypical cell characteristic of the disease).

CASE 9.—Case 9 is practically identical with Case 1, except that the azure granulation is not found in so many cells and is finer than in the cells of Case 1. Some of the plasma cells have rather diffuse nuclei which gives them a structure approaching that of the Türk irritation form.

TYPE II CASES

The next series of cases belonging to the group reported here are those included in our Type II. They include Cases 2, 4 and 7, and one outside case, already reported by Dr. J. G. Cross,[12] which we were permitted to study.

All of the cases of this series have a strikingly similar blood picture, which is characterized by the presence of atypical cells having a different morphology from those of Type I. There are slight gradations between the extremes of the two types, so it is likely that these morphologic characters are of slight importance.

An atypical cell of this series is illustrated in Figure 7, which represents the characteristic cell of Case 4. The slight variations from this type seen in the other cases will be pointed out in the notes on those cases.

The nucleus of Figure 7 is somewhat similar to that of a plasma cell. The chromatin strands are very coarse, and there are several dense, rounded or angular masses of chromatin among them. The arrangement of chromatin in dense masses is quite characteristic of the nuclei of plasma cells derived from lymphocytes, and the nuclei of many of the atypical cells of this series approach the plasma cell type more or less. They have more of a washed appearance, and the blocking of the chromatin is not so pronounced as in the plasma cell, but it may be more evident than is the case in Figure 7.

These considerations alone indicate that the cell of Figure 7 should be classified with the lymphocytes, and this conclusion is supported further by the fact that in all of the cases it is possible to build up a complete series of intermediate stages between the larger and medium-sized lymphocytes and the atypical cells having lymphocyte or plasma cell nuclei.

The cytoplasm in this series (Fig. 7) is very different from that of the cases belonging to Type I (Figs. 1 to 6). It has fewer vacuoles and its spongioplasm has a smoother appearance which does not give the foamy, spongy and stippled effect noted in the cells of Type I. It is generally less basophilic, and there is a more even mixing of spongioplasm and hyaloplasm. Figure 7 illustrates the tendency of the basophilic portion of the cytoplasm to be arranged in the form of broad bands radiating from the nucleus. This arrangement was striking in many of the cells of Case 4, but was not noted in the other cases of the series.

The cell body is generally wider than in the cells of Type I, and the nucleus is rarely lobulated. In Case 4, the nucleus seems to be quite fragile, for in most of the cells it is damaged somewhat and is generally squeezed out to one margin of the cell. This occurs in many different slides, so the damage is probably not due to the manner in which the smear was made.

Case 4 contains about a normal percentage of large mononuclears with lobulated nuclei and fine azurophil granulation in the cytoplasm.

Cases 2 and 7 are also of Type II, as is also the case reported by Dr. Cross.

CASE 2.—The atypical lymphocytes are practically identical with those of Case 4, except that there are more cells with narrow cytoplasm. There are few normal small or medium-sized lymphocytes, although one sees an occa-

sional medium-sized lymphocyte with a very narrow cell body but with a mature nucleus. There are no immature cells. The cytoplasm of the atypical cells is pale, as shown in Figure 7, but contains irregular basophilic areas in place of the basophilic streamers radiating from the nucleus. There are few cells with azurophil granules; those with granules contain from 1 to 3 of them. A few monocytes with lobulated or indented nuclei and fine azure dust in the cytoplasm, and transitional stages between these and the large lymphocytes are present. Eighteen days after the first examination, the atypical cells had practically disappeared from the blood. In this respect the case differs markedly from Case 1.

CASE 7.—The atypical cell is a large, wide-bodied cell with the nucleus of a medium-sized lymphocyte. The cytoplasm contains cloudy, basophilic areas which, however, do not radiate from the nucleus as in Figure 7. There are large vacuoles in the cytoplasm of some of the cells, and some cells contain very large, round azurophil granules. Cells with lobulated nuclei are scarce. An occasional atypical cell was found whose nucleus contained one or more nucleoli. But this was the only sign of immaturity, for in other respects the nucleus was that of the ordinary medium-sized lymphocyte. There are a few normal small and medium-sized lymphocytes and all transitional stages between them and the atypical large cells. These transitional stages are so numerous that there is no question in this case that the atypical cells are derived from lymphocytes.

Another case which we were permitted to study belongs in this series. It is the case reported by Dr. Cross as Case 1 of his series. The blood picture is almost similar to that of our Case 4, and the atypical cells are like the one shown in Figure 7, except that the cloudy basophilic areas do not radiate from the nucleus. The nucleus of a great many of the cells is very much like that of Figure 7. The chromatin blocks are distinct, and in many of the cells the nuclei are of the plasma cell type, although the cytoplasm is not like that of a plasma cell. Few of the nuclei are lobulated, and there are not many vacuoles in the cytoplasm. None of the nuclei show signs of immaturity, so the blood picture does not suggest leukemia.

COMMENT

All of the cases of our Types I and II are characterized by the presence of atypical cells which are clearly modified lymphocytes, or mesolymphocytes of Pappenheim. The abnormal characters are due to greater maturity and functional activity of the cells. Only occasionally are signs of immaturity present, and then they are never sufficient to confuse the picture with that of leukemia. Such signs were noted in Cases 2, 4, 5 and 7. In Case 2 there was an occasional medium-sized lymphocyte with a very narrow cell-body, but with mature nucleus. Case 4 was marked by extreme fragility of the pachychromatic (coarse structured) nucleus. In Cases 5 and 7, there were a few cells with nucleoli in an otherwise normal lymphocytic nucleus. Case 9 had a few plasma cells approaching the Türk irritation form, that is, with leptochromatic nuclei.

TYPE III CASES

Our Type III includes cases showing more leukemic features than any of those described under Types I and II. We have only one case (Case 3) to report under this heading. This case is also marked by

the presence of rather large atypical cells which in general are somewhat similar to those of Case 1 (Figs. 1 to 6). The cytoplasm is vacuolated and in some cells it is quite basophilic (Fig. 10). In the larger cells (Figs. 8 and 9), there is usually relatively more hyaloplasm, but the distribution of the spongioplasm remains about the same, in which respect the case differs markedly from those of Type II (Fig. 7).

The leukemic features are of chief interest in this case. Possibly 1 per cent. of the lymphoid cells contain a single large vacuole with an azurophil rod, in addition to smaller vacuoles distributed rather evenly throughout the cytoplasm. The larger vacuole is located within an indentation of the nucleus. One such cell is illustrated in Fig. 11, from which it is seen that the nucleus is that of a typical mesolymphocyte. Azurophil rods or fibers located in large vacuoles are features which have been reported in many cases of acute leukemia, especially in those of the lymphoidocytic (myeloblastic) type.

The nuclei of some of the atypical cells are dedifferentiated to such an extent that some of them closely approximate the lymphoidocytic type. Figure 8 is one such cell with a diffuse, vacuolated nucleus having three nucleoli. Comparison of this cell with those of Figures 12, 13 and 14 from a case of acute lymphatic leukemia shows that its nucleus is close to that of the stem-cell. It resembles closely the nuclei of Figures 12 and 14.

The smears contain numerous intermediate stages leading from the cell with immature nucleus to cells having nuclei like the one of Figure 11, which is a typical, completely differentiated lymphocyte nucleus. In the series which we have illustrated, the nuclei of Figures 9 and 10 are intermediate between those of Figures 8 and 11.

An occasional neutrophilic myelocyte was found in the blood of this patient and also a small number of medium and small lymphocytes with very narrow cell-bodies and indented or slightly lobulated nuclei.

The clinical features of this case were clearly against leukemia. The hematologic report was also negative for leukemia on account of the small number of immature cells and the presence of numerous lymphocytic plasma cells. These are cells with nuclei having coarse, distinct blocks of chromatin, a character which is usually pronounced in plasma cells derived from lymphocytes. These cells may occur in lymphatic leukemia (Naegeli), but they are usually not numerous. The Türk irritation form of plasma cell with diffuse myeloblastic nucleus may be abundant in various forms of leukemia, especially in those of the myelogenous type.

Naegeli was also able to decide against leukemia in two of his cases on account of the numerous plasma cells present. But Naegeli warns against the assumption that the presence of a few plasma cells excludes leukemia.

Sternberg [15] states that plasma cells do not occur in chronic leukemia, except where there is a coexisting inflammatory process. They do occur in acute leukemia, and this is one of Sternberg's reasons for believing that acute leukemia is an infectious process and not a true leukemia. He says that in chronic lymphatic leukemia plasma cells may be found separate from the leukemic infiltrations, especially in association with ulcerative processes.

In our own case (Case 3), there were not enough immature cells to suggest acute leukemia, while the sudden onset of the disease and the clinical findings, together with the occurrence of plasma cells in the blood were against chronic lymphatic leukemia.

DIFFERENTIAL DIAGNOSIS

Although the blood picture varies considerably in the three types of cases which we have reported, it has been shown that there are certain characteristic features which distinguish them from acute leukemia. This is true even in Case 3, in which the leukemic features were more pronounced than in the other cases. In this case, as in all the others, there are predominating atypical lymphocytes which give the blood its special character.

The morphologic features which characterize the atypical cells are largely cytoplasmic, but the nucleus may also be involved, as is shown by those cases in which the nucleus approaches the plasma cell type. In Case 3, we see that decidedly immature lymphocytes with leptochromatic nuclei and nucleoli may show cytoplasmic characters similar to those of the atypical cells derived from fully differentiated mesolymphocytes.

The atypical cells show some plasma cell characters which are more pronounced in some cases than in others. They may, therefore, be described as "abortive plasma cells." They are different from those seen in acute forms of leukemia, which are usually of the Türk irritation form.

In addition to the "abortive plasma cells," there may be other atypical cells, few in number, but with some leukemic characters. They and cells with immature leptochromatic nuclei are more abundant in acute leukemia than they were in any of our cases.

As far as the blood is concerned, there may be greater danger of confusing some of our cases with chronic leukemia than with the acute form. We have one good example of this possibility in a case of chronic lymphatic leukemia which is now under daily observation. The total count in this case has varied between 27,000 and 62,000, with the usual high percentage of lymphocytes. There are few immature cells, and on certain days the majority of the cells are of the type

shown in our Figure 7. The history, clinical findings and rapid changes in the cytology of the blood serve to distinguish this case from those in the group which we are reporting. On the other hand, the special characters of the cells which we have called atypical cells or abortive plasma cells, the small number of immature cells and cells showing other leukemic features, as well as the clinical findings, differentiate our cases from acute leukemia.

Total leukocyte counts and differential counts which do not distinguish between the different types of lymphoid cells present are of little value in deciding for or against acute leukemia.

One of our own cases and two outside cases referred to the writer for hematologic diagnosis may be cited in support of this statement. In spite of the fact that the total leukocyte count and the percentage of lymphocytes were about the same in the three cases, they represent three different types of disease. Although the counts were similar, the cytology was different in the three cases. Both the clinical findings and the counts pointed toward acute leukemia, which was suspected in all of these cases. Study of the blood cytology, however, showed only one of them to be leukemic. This checked with the final outcome of the cases.

The first case is our Case 1 (Figs. 1 to 6) which has already been described in detail. When the blood was first examined soon after the onset of the disease, there were 3,000 leukocytes with 83 per cent. lymphocytes. Five days later there were 92 per cent. lymphocytes. That these were not of the leukemic type has already been shown.

The next case was one of mouth infection with fever and extensive ulceration of the mouth and tongue. Smears from the ulcers contained Vincent's organisms. There were 3,200 leukocytes with 85 per cent. lymphocytes. Twelve days later, the total count had dropped to 2,600 leukocytes and 92 per cent. lymphocytes.

Cytologic study showed that the case was not leukemic and that it did not belong with our group of nine cases of benign lymphocytosis. There were a few atypical monocytes, but the lymphocytes were normal, except for an occasional large leukocytoid form somewhat similar to the one shown in our Figure 7, but without the cloudy areas. The azurophil granulation when present was normal. There were no immature cells. Large and medium-sized lymphocytes predominated, but there were a few small ones. The patient made a complete recovery and the blood returned to normal in about one month.

The third case with a similar total count and percentage of lymphoid cells was one of acute lymphatic leukemia. The case ran a clinical course typical for that disease and diagnosis was confirmed by histologic examination of the organs.

The first differential count in this case gave 84 per cent. lmyphocytes with a total leukocyte count of 3,200. The total count fluctuated between 3,000 and 5,000 for the next six days and began to rise on the seventh day, reaching 17,500 on the tenth day, which was the day before death. The percentage of lymphocytes gradually increased until it reached 99 per cent. the day before death.

Clinically, there was little to distinguish this case from the case of mouth infection discussed above, except that there was less ulceration in this case. The swollen and sore gums were at first ascribed to Vincent's gingivitis and pyorrhea. Leukocyte counts were similar in both cases when first seen, and anemia was not pronounced in either case. In the leukemic case, there were three million red cells and 70 per cent. hemoglobin the day before death.

The blood cytology of the leukemic case was totally different from that of either of the other two, showing a low total leukocyte count. This blood contained great numbers of atypical lymphoid cells in which the abnormal morphology was clearly due to immaturity and lack of differentiation. The number of such cells increased steadily with the progress of the disease until finally 85 per cent. of the lymphoid cells were immature lymphocytes.

We have illustrated three cells from this case in Figures 12 to 14. Figure 13 is probably the most immature cell of the three, but Figures 12 and 14 are close to the stem-cell. Comparison of these cells with those of Figures 1 to 6 from our Case 1 will immediately show the difference between morphologic changes due to immaturity and those due to other causes.

The blood of this leukemic case is of special interest and importance, because it contains all the intermediate stages between cells similar to the myeloblast of Naegeli and normal, fully differentiated lymphocytes. Discussion of this case, however, is reserved for a later paper, when the case will be reported in detail. For literature on cases of similar hematologic importance from the standpoint of the monophyletic theory of blood cell relationships, the reader is referred to the papers by Fineman,[27] Citron[28] and Du Toit.[29]

These three cases furnish a good illustration of the fact that the terms "lymphoblast" and "germ center cell," which have been used in the descriptions of benign lymphocytosis with adenoid hyperplasia, should be used with caution. The term "lymphoblast" may be justi-

27. Fineman, S.: A Study of Microlymphoidocytic Leukemia, Arch. Int. Med. **29**:168 (Feb.) 1922.

28. Citron, J.: Ueber zwei bemerkenswerte Fälle von (akuter) Leukämie, Folia Haematol., Arch. **20**:1, 1915.

29. Du Toit, P. J.: Beitrag zur Morphologie des normalen und des leukämischen Rinderblutes, Folia Haematol., Arch. **21**:1, 1916.

fied for cells like those shown in Figures 12 to 14, or even for a cell like that of Figure 8, if by lymphoblast is meant a cell whose nuclear structure indicates immaturity or lack of differentiation. Such cells, however, are not the type found in the germ centers of normal lymph nodes, and they are not necessarily the mother cells of the lymphocytes. They are abundant in acute leukemias, although the dedifferentiation does not necessarily reach back as far as the cells of Figures 12 to 14.

The finding of an occasional immature cell, as in our Case 3 (Figures 8 and 9) does not warrant a diagnosis of acute leukemia, even though the clinical picture should point in that direction. In chronic lymphatic leukemia there may be few immature cells, so that the diagnosis of that condition will frequently have to depend on other findings.

A lymph node was obtained from one of our cases (Case 7). In structure it seems to be similar to the nodes described by Sprunt and Evans, who removed nodes from three of their cases and found them to be very hyperplastic with some obliteration of structure. They differed from leukemic nodes only in the degree of hyperplasia.

The node from our case was hyperplastic, but showed small remains of follicles at the periphery. The peripheral sinuses were comparatively free, and there was no invasion of the capsule. The interior of the node was quite diffuse, with large areas of extremely small lymphocytes. Scattered here and there through the node, there were groups or single large lymphocytes with extremely basophilic cytoplasm, thin nuclear membranes, little chromatin and prominent nucleoli. These must be regarded as immature lymphocytes. The atypical lymphocytes of the blood could not be recognized, which seems to indicate that the atypical characters are assumed after the cells reach the blood.

The proliferation of the reticulum of the medullary sinuses noted by Longcope in the nodes of two of his cases was not seen in our case.

Comparison of this node with one from a case of chronic lymphatic leukemia shows only slight differences. The leukemic node shows some large germ centers, but no definite follicles; the peripheral sinuses are filled with lymphocytes, and there is slight invasion of the capsule. The distinct areas composed of extremely small lymphocytes are lacking in the leukemic node. In other respects, the two nodes are almost similar.

SUMMARY OF BLOOD STUDIES

Cytologic study of the blood in nine cases of benign lymphocytosis accompanied by adenoid hyperplasia has shown that the blood picture is sufficiently characteristic to warrant inclusion of all of the cases in one large group. The blood is characterized by the presence of a rela-

tively large number of atypical "leukocytoid" lymphocytes, which show sufficient variation in structure to suggest division of the cases into three types. The abnormal cell characters may be interpreted as being due to higher differentiation and special cell activity. In one case, these characters were combined with the nuclear signs of immaturity in a few cells. The blood of this case contained some other leukemic features, but they were not sufficient to warrant a diagnosis of acute leukemia.

Special attention was given to comparison of these specimens of blood with the blood picture in acute leukemia. In every case, it was possible to determine the nonleukemic nature of the blood, even though the clinical picture suggested acute leukemia.

A detailed comparison was made between one of these cases and one case of acute lymphatic leukemia having a total leukocyte count and lymphocyte percentage similar to our Case 1. A case of mouth infection with similar counts is described, and it is shown that the blood cytology is totally different from that of the leukemic case and from the group of cases of benign lymphocytosis. All three cases showed clinical symptoms of acute leukemia, but the blood picture differed in each case, and was sufficiently characteristic to permit correct diagnosis.

THREE FATAL ADULT CASES OF MALABSORPTION OF FAT

WITH EMACIATION AND ANEMIA, AND IN TWO ACIDOSIS AND TETANY *

HERRMANN L. BLUMGART, M.D.
BOSTON

The first step toward the treatment of a disease is the recognition of its existence. In the last seven years at the Peter Bent Brigham Hospital, there have been three cases which were not in accord with any hitherto recognized diagnosis, and which, because of the similar signs, symptoms, course and postmortem findings, strongly suggested a definite disease entity. Study of these cases has yielded little knowledge of the underlying etiologic factors. Because of this fact, these cases are presented, in the hope that similar cases will be more easily recognized, and more fruitful effort result.

REPORT OF CASES

CASE 1.—*History.*—A. J. N., aged 42, married, a piano-case maker, entered Peter Bent Brigham Hospital, Dec. 20, 1916, complaining of weakness and gaseous distension of the abdomen. His family, marital, and past history presented no significant data. His habits were excellent. He was born in Sweden, and had lived in Boston for twenty-five years. He had usually enjoyed good health. His illness dated from one and one-half years before admission, when, without evident cause, he had suffered from watery diarrhea. The stools numbered from four to five daily and never contained macroscopic blood. At the onset of the diarrhea, he was troubled by considerable epigastric distention, "sour stomach," and borborygmus. The diarrhea ceased after four months, but the gaseous distention persisted. He continued to work, but tired more easily.

Six weeks previous to entrance, he became noticeably short of breath, and observed that his feet swelled occasionally. Three weeks previously, along with a continuation of his dyspnea, he became increasingly weak, and, one week before coming to the hospital, was finally forced to stop work. The appetite was excellent, the bowels moved once a day, and he suffered no pain.

Physical Examination.—The patient was well developed, but thin. He lay quietly in bed, in no evident pain or discomfort. The face was somewhat emaciated, and there were several areas of vitiligo about the chin and throat. The skin was slightly yellow, pale and dry. The lips were pale, the tongue smooth, slightly reddened and shiny. The heart was normal, the rate, 80 per minute. Systolic blood pressure was 98, diastolic, 40. Physical examination of the lungs was negative save for a few dry râles at the right base, and a harsh expiratory grunt audible over all the front and back. The abdomen was rather full and distended, and tympanitic throughout. There were no masses, or areas of spasm or tenderness. The reflexes of the arms and legs were normal. Moderate soft edema was evident over both ankles. Ophthalmoscopic examination showed normal fundi. The temperature, respiration and pulse were normal.

---

* From the Medical Clinic of the Peter Bent Brigham Hospital.

Laboratory Findings.—Nine complete blood examinations during the patient's forty-nine day stay in the hospital showed the hemoglobin to average 73 per cent.; the red blood count, 2,900,000; the white blood count, 5,000. The differential count averaged: polymorphonuclears, 65 per cent.; lymphocytes, 30 per cent.; transitional cells, 5 per cent. There were no eosinophils, mast cells or myelocytes. The red blood cells showed considerable variation in size, with many microcytes and macrocytes, slight variation in shape, slight polychromatophilia, no normoblasts or stippling.

Four of the eight urine examinations showed the slightest possible trace of albumin, with occasional hyaline casts, twice. The phenolsulphonephthalein excretion was 47 per cent. in two hours.

Thirteen stool examinations were made. The bowel movements averaged two per day. All stools were gray, unformed, pasty and shiny. They contained no macroscopic blood, mucus or parasites. Microscopically, numerous sheafs of fatty acid crystals, and, after heating with acetic acid, numerous fat droplets and needle crystals, were evident. No pus or ova were present. The benzidin reaction was persistently negative. The mercuric chlorid test for bile was always strongly positive. The increase in fat and fatty acids gave a striking contrast to the stools of other patients on the same house diet.

Proctoscopic examination showed no apparent atrophy of the mucosa of the rectum.

Results of Blood Analyses

	Whole Blood, Gm. per 100 C.c.	Plasma, Gm. per 100 C.c.
Lecithin:		
Normal, fasting	0.30	0.22
Patient, Before meal	0.24	0.12
Patient, After meal	0.26	0.12
Cholesterol:		
Normal, fasting	0.21	0.22
Patient, Before meal	0.15	0.12
Patient, After meal	0.15	0.12
Total Fatty Acids:		
Normal, fasting	0.36	0.38
Patient, Before meal	0.51	0.29
Patient, After meal	0.40	0.30

Gastric analysis of the fasting content and specimens withdrawn at forty-minute intervals following an Ewald test meal showed a persistent anacidity and a low total hydrochloride content, never requiring for titration more than 14 c.c. of tenth normal sodium hydroxid per hundred cubic centimeters. Microscopic examination of the fasting contents showed no food residue, no sarcinae, yeast cells or Oppler-Boas bacilli. The benzidin reaction was negative.

Roentgen-ray studies of the gastro-intestinal tract revealed no abnormalities. The actual emptying time of the stomach was three and one half hours.

The patient raised a moderate amount of mucoid sputum, which on two occasions showed no tubercle bacilli. Both fresh and digested specimens were examined. The Pirquet test was but slightly positive at the end of twenty-four hours. Roentgen-ray examination of the chest showed cloudiness of the superior mediastinum, more marked on the right, and obscuring somewhat the lung field in the region of the right apex. This was suggestive of large mediastinal glands.

The patient's blood sugar was found to be 12 mg. per hundred cubic centimeters. The basal metabolic rate was found on two successive occasions to be −7 and −8. Seventy-two minutes after eating 413 gm. of beefsteak, the metabolic rate had risen to +15. After 147 minutes, it was +14.

The Wassermann reaction on the blood serum was negative.

A study of the patient's ability to digest fat was attempted. He was given 100 gm. of fat in the form of 20 per cent. cream and butter. Blood samples were analyzed for lecithin, cholesterol and total fatty acid content both before and five hours after the meal. The results are summarized in the accompanying table.

It will be noted that the lecithin, cholesterol and total fatty acid content of the whole blood was low; likewise, the cholesterol and lecithin content of the plasma was below the normal amount. Of greater significance is the fact that none of the amounts were found to be increased following the ingestion of the meal.

On another day, the duodenal contents were withdrawn on a fasting stomach, and the ability to digest olive oil, boiled and unboiled starch, and casein was studied. In each instance, the control tubes, containing the foregoing substances minus the duodenal ferments, showed no change after eighteen and thirty hours' incubation; whereas, practically complete splitting was accomplished by the patient's duodenal ferments. Quantitative estimations of the pancreatic ferments showed the amylase and trypsin content to be normal, the lipase slightly less than normal.

The fat content of the blood was also studied. One hundred and seventy cubic centimeters of blood was withdrawn and carefully mixed with four volumes of 95 per cent. alcohol. Bloor's method for determining the presence of unsaturated fatty acids was employed. The fat took up no iodin, indicating the absence of unsaturated fatty acids.

On a standard Schmidt-Strassburger diet, the fat output in the stools was found to be 19 per cent. of the intake; whereas, the normal was considered to be about 5 per cent. Of the fat present in the stools, about 77 per cent. was present as fatty acids and soaps. These tests would indicate satisfactory digestion, but incomplete absorption.

Hydrochloric acid was given over a considerable period without appreciable effect.

Diagnosis.—Because of the blood picture and the pallor, the diagnosis of pernicious anemia was considered, although the blood picture was not entirely characteristic. The degree of prostration, moreover, was out of proportion to the anemia. This latter fact, together with the presence of pigmentation, low blood pressure, anemia and fatty stools, suggested Addison's disease with intestinal tuberculosis.

During the stay in the hospital, the patient's strength improved somewhat; and he was finally discharged on the forty-ninth day with the diagnoses: pernicious anemia? Addison's disease? tuberculosis of the retroperitoneal lymph nodes?

Course and Readmission.—After leaving the hospital, Feb. 6, 1917, the patient had about three bowel movements a day, and was troubled by considerable epigastric fulness and borborygmus. He became progressively weaker, his appetite failed, and he lost so markedly in flesh that, on readmission, April 8, his weight, which on discharge had been 58 kg., had fallen to 43 kg. Physical examination, save for increased wasting, was unchanged. The stools retained their previous characteristics. Examination of the urine was negative on four occasions.

Examination of the blood showed the hemoglobin to the 62 per cent.; the red blood cells, 2,568,000; the white blood cells, 3,800 per cubic millimeter. The differential count was: polymorphonuclears, 70 per cent.; lymphocytes, 30 per cent. The red cells showed moderate variation in size, slight variation in shape, polychromatophilia, rare stippling and no normoblasts. The temperature, pulse and respiration were normal.

The patient remained in the hospital eleven days before he died. During this time, the temperature ranged between 96.4 and 98.8 F., averaging about 97.6. The pulse varied between 80 and 90, the respirations between 16 and 20. During his stay he complained of no pain or discomfort, and he increased in weight from 43.2 to 44.0 kg. On the day before his death, physical examination revealed the development of a few small red spots about the size

of a dime near the tip of the tongue, which the patient stated had become rather painful. The heart was slow and regular. The lungs were clear save for a few râles at both bases posteriorly. The abdomen was tympanitic throughout, not distended and very slightly tender on pressure. No masses were felt. The liver and spleen were not palpable. Mentally, the patient was clear and alert.

At 3:30, the following morning, he was unable to talk, eyes wide open, respirations rapid, pulse weak. At 5 o'clock, the heart was absolutely irregular both in force and rhythm, with an apex rate of 120. Respiration continued to be rapid but regular. The lungs were full of coarse râles. The patient soon lost consciousness, and died at 7:10 a. m., evidently from cardiac failure.

Necropsy Findings.—Necropsy was performed six hours postmortem by Dr. E. W. Goodpasture. It was restricted to the abdomen. On abdominal incision, the complete disappearance of subcutaneous and intra-abdominal fat was evident. There was no excess of fluid. The peritoneal surfaces were smooth and normal. The most striking feature was the enlargement of the mesenteric lymph nodes.

The liver appeared normal. The capsule, which was smooth, was a dark, purplish brown. The weight of the liver was 1,050 gm. The biliary passages were normal. Microscopically, the beam-work of liver cells appeared rather thin, and showed some increase of mononuclear cells in the sinusoids.

The spleen was small, weighing 70 gm. On section, the blood vessels and fibrous tissue trabeculae were very prominent; whereas, the splenic follicles were small.

The esophagus and stomach were normal, except for slight injection of the blood vessels of the gastric mucosa. Beginning at the duodenum and extending to the ileocecal valve, numerous granules were to be seen over the entire surface, appearing as minute elevated grayish dots about 1 mm. in diameter, projecting above the surface. In every respect, they gave the appearance of solitary lymph follicles. They were, however, far more numerous than the normal. No Peyer's patches were noted; but, especially in the upper portion of the bowel, from ten to twelve of these small granules were irregularly grouped at intervals. These groups did not closely resemble Peyer's patches. The contents of the small intestine consisted of a small amount of yellowish mucoid material.

Numerous sections of the small intestine were examined microscopically. All showed a thin, loose, edematous submucosa with dilated vessels beneath the lymphatics and veins. In places, the edema was more or less circumscribed, forming slightly elevated nodules. The mucous membrane was thin and somewhat atrophic. All the follicles were large, and the villi short, with many lymphoid cells in the interglandular tissue. There was, however, no leukocytic infiltration.

All the mesenteric lymph nodes were considerably enlarged. Grossly, they gave the appearance of hyperplasia, being gray, semitranslucent, and uniform on cut section. The lymphatics, though visible, were not prominent. The lymphatic enlargement was confined to the small intestine and to the mesenteric lymph nodes, the glands elsewhere appearing normal. There was no evidence at necropsy of superficial glandular enlargement or of hyperplasia of the lymphatic elements of the spleen. All the mesenteric lymph nodes examined microscopically were in a high degree edematous, with dilated sinuses and a prominent reticulum. The peripheral sinuses of the nodes were small. The lymphoid tissue was abundant. Solid masses of lymphoid cells filled the centers corresponding to the follicles. About these, the cells in the reticulum were rather closely packed. There were no dilated lymphatics in the surrounding nodular lymphatic tissue, and no germinal centers were evident.

The large intestine was greatly distended with gas and soft, pasty, sticky fecal material, which, from its pale, gray color, was apparently very fatty. The mucosa of the large bowel was normal, without lymphatic hyperplasia.

The kidneys, save for slight congestion and the presence of pin-point yellowish, opaque dots, were normal, macroscopically and microscopically.

The bladder, seminal vesicles and prostate were likewise normal.

Pathologic Diagnosis.—Emaciation, hyperplasia of the lymphatics of the small intestine and mesenteric glands, atrophy of the liver and spleen, congestion of the kidney and Meckel's diverticulum were diagnosed.

CASE 2.—*History.*—M. R. R., a woman, aged 44, unmarried, who had always lived in New England, entered the hospital, Feb. 16, 1917, complaining of abscesses of the feet, ulcers of the cornea, and constipation followed by diarrhea.

The family history showed that her father had died at 74 of angina, while her mother was still living at 80. There was no family history of cancer, diabetes, tuberculosis or hemophilia. Several members of the family were said to have suffered from gout. The personal habits were good.

The patient had usually enjoyed good health. She had had measles twice, chickenpox, whooping cough, a light attack of influenza and occasional sore throats. There had been no known exposure to tuberculosis. She had sustained no injuries, nor had she undergone any operations. The appetite was fair. There was habitual constipation. Catamenia was established at 15, recurring irregularly every three weeks and lasting three or four days. At the age of 24, following a fall into the water, she experienced a cessation of her periods, and there had been no subsequent flow. There had been no incidents indicative of nervous derangement.

The best weight had been 125 pounds (56.8 kg.); the weight, one and a half years previous to admission, was 85 pounds (39.6 kg), and on admission, 71 pounds (32.2 kg.).

The present illness dated from two years previous to admission, when the patient noted that the ankles were slightly swollen and that she was losing her customary vigor. She was not incapacitated. Swelling of the feet and ankles gradually became so pronounced that she consulted her physician, who could find nothing definitely accountable for the edema. One year previous to entrance, the swelling diminished, only to recur eight months previous to entry. Four months previously, an abscess appeared on the anterior surface of the right ankle, followed by a similar one on the dorsum of the left foot, and, a few weeks later, by a small abscess just below the left knee. All of these were incised, but failed to heal satisfactorily. One week before admission, the eyes seemed somewhat blurred and watery. On examination, a corneal ulcer was found, and ointment and hot compresses were prescribed. She had experienced no pain whatsoever. The bowels had moved somewhat more freely than usual, following the administration of cathartics by her physician, but the movements were not watery.

Physical Examination.—The patient was a small extremely emaciated, middle-aged woman. She was mentally clear. The skin was pale, smooth, dry and somewhat inelastic, this inelasticity being due in part to the practical absence of subcutaneous fat. The face, with prominent malar eminences and temples and sunken cheeks, presented a cadaverous appearance. Just to the mesial side of the center of the right eye was a corneal ulcer, the size of a pinhead. There was a moderate degree of photophobia and lachrymation. No edema of the lower lids was evident. The lips were of normal red color, the teeth in excellent condition. The tongue, which was clean, smooth and glossy, protruded in the midline, with a moderately coarse tremor. The thorax was symmetrical, flat and emaciated in the extreme, with the clavicles extending high above the surrounding tissues. The apex impulse could be neither seen nor felt. The right cardiac border measured 4.5 cm., the left, 10 cm., from the midsternal line. The first sound was distant, feeble, dull and muffled, the second, rather loud and ringing. The radial pulses were equal, regular and synchronous. The vessel walls were palpable but not sclerosed. The systolic blood pressure was 114, the diastolic, 80. The lungs were normal. The abdomen was level and symmetrical, but was held so tensely as to make satisfactory palpation impossible. The vessels of the abdominal wall were moderately dilated, but not sufficiently so to indicate compensatory circulation. The liver, gallbladder, spleen and

kidneys were not palpable. The lymph glands, with the exception of one small, shotty nodule on the left sternocleidomastoid muscle, were not palpable. All the bones seemed essentially normal.

The arms were markedly emaciated, but the nails showed no trophic disturbances. There were no tremors, involuntary athetoid or choreiform movements. The fingers were not clubbed. The radial periosteal, biceps and triceps jerks were active and readily elicited. The skin over the backs of the hands and over both elbows was reddened, thickened and blotchy.

The legs, feet and ankles were moderately edematous, pitting readily on pressure. On the anterior aspect of both external malleoli were two ulcers, 0.5 cm. in diameter, shallow in type, with clean, overhanging edges. A smaller ulcer was to be seen over the left infrapatellar ligament. These ulcers were discharging a slight amount of yellow pus. Both feet were practically the temperature of the room, the coldness extending upward to about two hands' breadth above the ankles. The reflexes were normal. Although on admission the patient's temperature was 97.8 F., during the evening, per rectum, it was no higher than 94.0 F. The pulse was 82, respiration, 20. The patient was seen by an eye consultant on the day folowing admission. He stated that the corneal ulcer was superficial, and due, probably, to general nutritional disturbance.

Laboratory Findings.—The urine was acid and clear, with a specific gravity of 1.018. It contained no albumin or sugar. The sediment showed a few leukocytes and occasional epithelial cells. The hemoglobin content of the blood was 75 per cent.; the average of four red cell determinations was 3,000,000. Although the color index was +1, the smear showed none of the characteristics of pernicious anemia. The white blood cells numbered 4,000 per cubic millimeter. Two stools were acid, yellow and watery, with much apparent mucus, but no evident blood. The benzidin test was moderately positive. No parasites or ova were evident on microscopic examination.

Course.—The morning of the second day, the patient, who had been bright, became dull and stuporous, with a pulse rate which had dropped to 44 per minute. Atropin was administered subcutaneously. By early afternoon, she was herself again, sitting up in bed, talking and joking. The heart rate had risen to 65. On the afternoon following the attack, the carbon dioxid in the alveolar air measured 24 mm. of mercury, but no acetone or diacetic acid was found in the urine. The patient was clear mentally, and recalled her condition of the earlier part of the day; she "could not understand why she had been so sleepy."

The third day following admission, she awoke at 5 a. m., and began to talk irrationally. The heart rate was 41; blood pressure, systolic, 86, diastolic, 64. Mouth, axillary, and rectal temperatures taken practically simultaneously showed a continuation of the low temperature of the previous day; namely, 89.0, 89.0, and 90.8 F., respectively. In order to obtain these temperatures, a special clinical thermometer was necessary. During the morning, the patient continued to be irrational. By 11 a. m., the heart rate had gradually risen to 88.

At noon, the patient was found in what appeared to be typical tetany; rigid, with feet very markedly extended and hands flexed, the thumb turned in on the palm, and the fingers tapering to a common point. There were no convulsive movements of the face, save at the onset of the tetanic symptoms, when the nurse noted convulsive twitchings of the left side of the face.

Electrocardiographic tracings showed Lead 1 to be nearly iso-electric, and the rate slow, with definite sinus arrhythmia. The condition of tetany persisted; respiration became much quieter, and ceased at 3:15 a. m.

Necropsy Findings.—Necropsy was performed eighteen hours postmortem by Dr. S. B. Marlow. On primary incision, the tissues were found to be markedly atrophied, containing no evident fat. The abdominal wall was extremely thin, the rectus abdominus muscles appearing as thin, tense bands.

The abdominal cavity contained 500 c.c. of a milky, white fluid. The entire peritoneum was pale and watery.

On removal of the sternum, the lungs were found moderately collapsed and wholly free from adhesions. The pleurae were everywhere smooth and shiny. The right lung was somewhat firmer than the left. The anterior surface of the right lung was pale and puffed out, the alveoli in these puffy areas being dilated and filled with air, which was easily expressed, leaving the lung collapsed. At the base of the right lung, there was an irregular, depressed scar, which on section was fibrous and tough. In the center, about 1 cm. below the surface, was a caseous nodule 5 mm. in size. At the apex of the left lung, there was a similar irregular, depressed scar, above which there were grayish yellow dots. Section through the lung at this point showed it to be firmer than normal. Section of the posterior portion of the left lung revealed a deep red, homogeneous surface. It was quite firm and inelastic, containing practically no air. There were, however, no areas of consolidation. Lobules of the lower lobe stood out distinctly, demarcated by milky white lines. The lower lobe of the right lung was similar to that of the left. Sections showed practically all the alveoli filled with red blood cells and fibrin. There was a moderate number of polymorphonuclear leukocytes scattered generally throughout the lung. Some of the alveoli seemed almost filled with these cells.

The heart was unusually small weighing 130 gm. The loosely adherent epicardium had a watery, translucent appearance. No fat was anywhere visible. The vessels stood out prominently. Numerous white streaks were seen in the epicardium, following the larger vessels, evidently lymphatics. The endocardium was everywhere smooth and pink, and heavily streaked with gray. The valves were normal. The papillary muscles were much flattened and atrophied. On section, the myocardium appeared a homogeneous brown. Microscopic examination revealed small muscle cells, the muscle bands being separated by edema. The interstices contained numerous vesicular bodies, and the nuclei of the cells were surrounded by considerable pigment.

The stomach was normally situated, contracted and of a normal external appearance. On section, it was found to contain much mucous material. The mucosa, which was thickened and markedly edematous, was seen microscopically to have undergone considerable postmortem change, with numerous fairly well preserved parietal cells still present. The chief cells were for the most part desquamated and disintegrated, but numerous round and plasma cells were found.

The intestines were light yellow, especially in the upper portion, where numerous yellow patches from 1 to 3 mm. in diameter were to be seen scattered diffusely through the wall. Those patches lying opposite the attachment of the mesentery seemed distinctly paler in color. Microscopically, the mucous membrane had undergone considerable postmortem change, with almost complete desquamation of the cells lining the villi. The loose connective tissue in the submucosa just beneath the muscularis contained numerous large mononuclear cells, and multinucleated giant cells containing a finely vacuolated cytoplasm. These cells apparently contained fat. The colon was small; the esophagus normal.

The liver was small, weighing 560 gm. Projecting from the lower edge of the right lobe was a typical Riedel's lobe. Above it, the liver capsule was thickened and fibrous. The liver capsule was firm and somwhat difficult to cut. On section, the surface was a homogeneous grayish brown, with distinct lobules, whose centers were a deeper color than the portal areas. On microscopic examination, the cell columns of one-half the lobule were atrophied, the cells being loaded with fine golden pigment granules. Because of atrophy of the cytoplasm, the nuclei, which were smaller and more deeply staining than the normal, appeared very numerous. The gallbladder was normal and free from adhesions.

The pancreas was a watery yellow, but normal in size and position. The cut surface was granular and yellow, but without any evident connective tissue increase. The pancreatic and acinar cells contained no zymogen, microscopically, but otherwise the pancreas appeared normal.

The spleen, which was small, weighed 30 gm. Its consistency was firm. On section the capsule was markedly thickened, the trabeculae prominent, and the malpighian bodies and blood vessels numerous. There was evidently little pulp tissue remaining.

The mesentery contained numerous milky dilated lymphatics, but practically no fat. The lymph nodes were soft, cheesy and enlarged, about the size of a pea.

The kidneys were unusually small and were embedded in a capsule which was loose and edematous. The right kidney weighed 80 gm., the left 60 gm. The capsule stripped with moderate difficulty, leaving a smooth pinkish yellow surface, in which fetal lobulations were pronounced. The cortex measured 5 mm. The striations were regular, and the glomerulae discernible. The pyramids looked normal. Microscopically, the glomerular spaces and kidney tubules were dilated, and filled with pink staining granular vesicular bodies. The picture was that of edema of the kidney.

The pelvic organs were small, fibrous and senile in type, without evident abnormalities. The ovary was microscopically normal.

The parathyroids were carefully dissected out and found to be normal in appearance. Likewise the thyroid and suprarenals presented no apparent abnormalities.

The thoracic duct was carefully explored and found to be free from obstruction anywhere in its course. It contained no fluid.

The bone marrow was a clear translucent yellow, evidently consisting chiefly of fat.

The pathologic diagnoses were brown atrophy of the heart, Riedel's lobe of the liver, hypostatic congestion of the lungs, chylous ascites, emaciation, atrophy of the spleen, bronchopneumonia and fat retention in the intestine.

Case 3. *History.*—F. W. G., married, a clerk, aged 32, entered Peter Bent Brigham Hospital, May 15, 1922, complaining of diarrhea and loss of weight. His family, marital and occupational histories were not significant. His habits were good. He had lived in Boston for about twenty years, after which he had spent one year in the South, East and West, before finally settling in the Middle West. He had not been in the South for about twelve years. He had had measles in early childhood, and scarlet fever at 10. Otherwise, his health had always been excellent. The bowels had always moved once daily, the appetite had always been excellent, and he had never suffered from gas, hematemesis, distress, colic, icterus or abnormal stools previous to the onset of his illness.

The patient considered himself perfectly well until sixteen and a half months previous to admission, when, without evident cause, he developed a painless diarrhea, with from six to eight loose, watery stools daily, without blood or mucus. One year previous to entry roentgenograms were taken of the gastro-intestinal tract and the patient was told by his local physician that the diarrhea was due to the appendix, which pressed against the stomach. His diarrhea continued, unaccompanied by any other gastro-intestinal symptoms; he lost 40 pounds (18 kg.) in weight, became worried and finally went to a hospital, asking to have the appendix removed. At operation, eleven months previous to his entry at Peter Bent Brigham Hospital, the appendix and the other abdominal organs were considered normal. He remained in the hospital ten days, and the wound healed by primary intention; but diarrhea persisted, and weakness increased. For the first time, he began to vomit practically everything he ate.

He attempted various forms of dietetic treatment without success, staying in one hospital as long as seven weeks. While there, he developed a single small ulcer on his tongue which persisted for one month, and the condition was diagnosed as sprue.

Eight months before admission to Peter Bent Brigham Hospital, he returned home weighing 85 pounds (39.6 kg.), a loss in eight and a half months of 85

pounds; that is, a reduction to one half his original body weight. On returning home, the vomiting ceased, although the diarrhea persisted. The patient ate heartily, and within two months regained 41 pounds (18.6 kg.). Five months before entry, he was impelled to consult another physician, who put him on a diet of 3 quarts (about 3 liters) of heated milk and three eggs daily. To this diet, lamb, steak, bread, etc., were gradually added. In three weeks, the number

Fig.1 (Case 3).—Extreme emaciation several days before death.

of stools was reduced to about three a day, and these assumed a semisolid character. He continued to lose weight slowly, however, and therefore came to Boston, two weeks previous to admission. His stools averaged three or four daily, becoming slightly looser. His appetite, which, throughout his entire illness had been remarkably good, failed him, and he decided to enter the hospital.

Physical Examination.—The patient was extremely emaciated. He lay comfortably in bed, mentally alert and cheerful. His features were sunken, with prominent bony eminences, which gave him a strikingly cadaverous expression. The skin was of normal color, dry, flabby and smooth. It had lost its elasticity, so that when pinched it retained its position for aperceptible interval before spontaneously resuming its former flatness. This property made it doughy to the touch. The lips and mucous membranes were moderately pale. The lungs and cardiovascular system were normal. The systolic blood pressure was 90, the diastolic, 70. The abdomen was slightly rounded, doughy, asymmetrical, with a definite tympanitic prominence to the left of the umbilicus. The scar of the old right rectus incision was evidently the result of healing by primary intention. There were no signs of fluid, and no abnormal masses, spasm or tenderness. Visible peristalsis was definite. No lymphatic enlargement could be demonstrated. Except for marked emaciation, the extremities were negative. Proctoscopic, rectal and ophthalmoscopic examinations were negative. The blood Wassermann reaction was negative.

The patient's temperature ranged from 97 to 99 F., averaging about 97.2 F. The pulse rate averaged about 70 per minute during the first few days, gradually rising toward the end to about 90. The respirations remained at about 20 per minute.

Laboratory Findings.—All of the fourteen stools examined were light yellow, and contained no parasites or ova, no fatty acid crystals, no gross or occult blood and no mucus. The number of bowel movements ranged from one to three a day, although on three occasions there were as many as five.

The hemoglobin content of the blood was 60 per cent., the red cell count, 2,050,000 per cubic millimeter. The white cells numbered 3,800 on admission. The polymorphonuclear cells were 45 per cent. of the total, the lymphocytes, 35 per cent., the large mononuclears (transitionals) 20 per cent. Many macrocytes were seen. Some red blood cells showed marked achromia, others, none. Four normoblasts were found. On three successive occasions during the patient's twenty-five day stay in the hospital before death, the white count varied from 4,000 to 5,400 per cubic millimeter. The hemoglobin (by Sahli's test) averaged 66 per cent. and the red blood cells averaged 2,500,000 per cubic millimeter.

The urine was always light yellow, with the slightest possible trace of albumin, but no casts, and only a few white cells. On three occasions, it was acid, on one occasion, alkaline.

Two examinations of phlegm which the patient raised on two different occasions were negative for tubercle bacilli.

On the fifth day in the hospital, gastric analysis, performed after an Ewald test meal, showed the absence of free hydrochloric acid in all specimens, and a total acidity ranging between sixteen and thirty-six. The fasting contents consisted of 20 c.c. of turbid, mucoid, slightly greenish fluid, containing microscopically many interwoven fungus filaments. There was no gross or occult blood.

Roentgen-ray examination of the chest showed normal diaphragm, heart and aorta. The lung fields were unusually clear. The ribs exhibited no evidence of any abnormality.

A barium sulphate enema showed the outline of the large intestine to be smooth everywhere, with fewer haustra than usual. All parts of the large intestine appeared to be dilated, the capacity being more than 6 quarts (about 6 liters).

Roentgen-ray study of the esophagus, stomach and small bowel revealed no evidence of any pathologic process.

An examination of the duodenal contents showed the proteolytic and amylolytic ferments to be well within normal limits; whereas, the lipolytic

enzyme titer was 0.6 of normal. The method used was that of McClure, Wetmore, and Reynolds.[1]

Course.—During the first few weeks of the patient's stay in the hospital, the clinical course was uneventful. He did, however, complain of dryness of the tongue, and experienced some difficulty in eating sufficient food to satisfy his caloric requirements. For the first week, he maintained his admission weight of 37 kg., but during the second week, he lost 1 kg.

On the eighteenth day in hospital, the arms felt stiff and numb; on observation, the arms and hands were found in the typical position of tetany. The feet showed no changes, but there was a positive Chvostek sign. The patient complained of no pain. He stated that he had observed exactly similar phenomena one month before entering Peter Bent Brigham Hospital, the condition lasting at that time two hours. By noon, the hands and arms relaxed, and a positive Trousseau sign was readily obtained. The blood carbon dioxid was 14.3 mm. of mercury; the blood calcium, 5.3 mg. per hundred cubic centimeters; the inorganic phosphate content, 2.6 mg. per hundred cubic centimeters. The urine contained no acetone or diacetic acid.

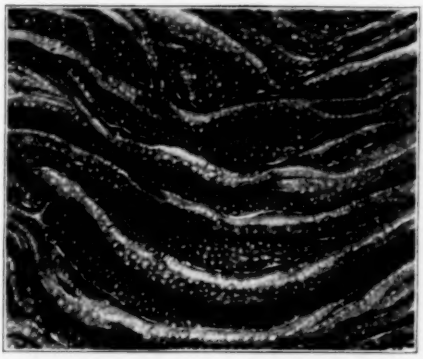


Fig. 2 (Case 3).—Gross appearance of duodenal mucosa, showing numerous granules due to phagocytes in the submucosa containing fat droplets.

The patient did not exhibit any return of the active signs of tetany, although Trousseau's sign could always be elicited. Six days later, on the 24th day, the cathodal closure contraction was obtained with 2 milliamperes, the cathodal opening contraction with 2.5 milliamperes, the anodal closure contraction with 2.25 milliamperes, and the anodal opening contraction with 2.25 milliamperes. The apparatus tested on three normal individuals gave the cathodal closing contraction with 6, 10 and 5 milliamperes, respectively. Despite the use of various diets and medications to combat the steady loss of weight, the patient became gradually more and more emaciated. In view of his precarious condition, on the 24th day of his stay, 500 c.c. of 10 per cent. glucose was given intravenously. It was hoped that, by repeated injections, from one third to one half of the caloric requirements could be introduced. He seemed to take it well, as he made no complaint and his pulse, respiration and temperature were found at half hourly intervals to be normal.

Suddenly, however, about one hour after the injection, he complained of numbness and coldness of the hands and feet; the respiration and pulse mounted

1. McClure, C. W.; Wetmore, A. S. and Reynolds, L.: New Methods for Estimating Enzymatic Activities of Duodenal Contents of Normal Man. Arch. Int. Med. **27**:706 (June) 1921.

to 40 and 120, respectively, and the face assumed an anxious expression. Believing that the introduction of a hypertonic solution had possibly resulted in an anhydremia, intravenous and subpectoral saline solution to the amount of 1,800 c.c. was given, without influencing the progress of the patient's condition. Before allowing the saline to flow, a few cubic centimeters of blood was withdrawn. The blood carbon dioxid combining power was found to be 14.3 mm. of mercury. Respiration became labored and occasionally hyperpneic. The abdomen was held stiffly, tracheal râles developed, and, at 12:30 a. m., the patient died.

Necropsy Findings.—Necropsy was performed nine hours postmortem, by Dr. W. S. Quinlan. The primary incision showed an absence of subcutaneous fat. The muscles were pale and atrophic. The peritoneal cavity contained no free fluid, but the intestines were lubricated by a clear, viscous fluid, which on staining showed many endothelial and a few polymorphonuclear leukocytes. There were no adhesions. The mesenteric lymph nodes were markedly enlarged, varying in size from 0.5 to 1.5 cm.

The pleural and pericardial cavities appeared normal. The heart was small, weighing but 180 gm. All the chambers, valves and chordae tendinae were of normal appearance, save that the myocardium was pale and soft, giving the impression of an atrophy with edema. This impression was substantiated microscopically. The spleen weighed 80 gm. It showed moderate wrinkling of the surface, but otherwise appeared normal.

Both grossly and microscopically, the stomach and duodenum were normal. The surface of the jejunum was pink, and was everywhere covered by grayish punctate that varied in size from a pinpoint to 1 mm. in diameter. These minute elevations simulating distended lacteals on a pinkish background gave a "furred tongue" appearance to the surface. In places, the gray granules were compactly arranged, forming spindle-shaped depressed areas similar to Peyer's patches in appearance, except that they extended along the long axis of the intestine opposite the mesenteric attachment to a point much higher than is ordinarily seen, and were larger in size, measuring 1 by 8 cm. Several sections, examined microscopically, showed dilated vessels and phagocytes in the submucosa filled with fat droplets. Over the lower 100 cm. of the jejunum, many roughly circular ulcers were seen, varying in size from 0.5 to 2 cm. The edges of the ulcers were well defined, slightly thickened and beaded with pinpoint grayish elevations. The floor of the ulcers was black, smooth and glistening, giving the appearance of being covered with mucous membrane. None of the ulcers seemed active.

The cecum was distended to about twice its normal size. The mucosa was dull gray, with a few solitary follicles scattered over the slightly thinned wall. The entire surface was coated with a layer of mucous approximately 0.5 cm. in thickness. Section through the wall of the intestine showed moderate thickening. Microscopically, the glands were distended with mucus, in places being sufficient marked to have caused actual atrophy of the epithelial cells lining the gland.

The pancreas, liver, gallbladder, suprarenals and genitalia exhibited no abnormalities. The left kidney was normal, the right presented a "V" shaped area of scarring, 1 cm. in diameter, evidently an old healed infarct.

The right lung appeared normal, but on section a calcified, nodular mass about 1.5 cm. in diameter presented itself, surrounded by gray, fibrous tissue. The left lung was likewise normal save for an area of scarring at the apex which measured 2.5 by 3 cm. Macroscopically and microscopically, the picture was that of healed pulmonary tuberculosis. The larynx, pharynx, tongue and thyroid presented no abnormalities. The brain, dural sinuses, accessory nasal sinuses, middle ears and pituitary were likewise normal.

The mesenteric lymph nodes were definitely enlarged and showed evidence, microscopically, of chronic lymph adenitis and hyperplasia.

COMMENT

These cases, presenting such hazy clinical outlines, evoked considerable interest and speculation. The asthenia, the gastro-intestinal disturbances and the anemia suggested Addison's disease. However, the asthenia was not in any case a primary symptom. Vascular asthenia, as reflected in the blood pressure, did not occur. In only one case was there any disturbance of pigmentation, and in that instance the condition was one of vitiligo rather than chloasma. Finally, the absence of active tuberculosis at necropsy and the presence of apparently normal suprarenal glands justify the exclusion of this possibility.

The anemia, with a high color index, the gastro-intestinal symptoms, the pallor, the gastric anacidity and the asthenia were in accord with the diagnosis of pernicious anemia. The absence of the characteristic blood picture, the marked loss of subcutaneous fat, and the postmortem findings made such a diagnosis untenable.

The presence of prolonged diarrhea suggested a bacillary dysentery and the colitis group of cases. The character of the stools, however, and the postmortem distribution of the lesions in the small intestine rather than in the large bowel, are not in accord with any of these diagnoses.

These cases, particularly the last one, possessed some of the characteristics of sprue. In the last case, the existence at one time of an ulcer of the tongue, the occurrence of an increased number of fatty stools, the anemia, the extreme wasting and the tendency to remission favored this diagnosis.

Other features did not lend themselves to this conception of the disease: 1. The last patient had never visited any endemic center. He had spent one year in the South, where sprue, though very rare, does occur; but this visit had taken place about eleven years previous to the onset of the symptoms; and a latent period of eleven years is difficult to accept.

2. The characteristic tongue lesions were absent. One year previous to the time he came under our observation, the patient had had a small ulcer on the tongue, lasting about one month. During the subsequent course of the disease, when the degree of activity of the condition should have become greatly increased, no lesions appeared. On the contrary, the patient, when questioned, did not complain of the slightest soreness of the tongue or buccal mucosa.

3. The stools were not characteristic. They were not "enormous, fermented, whitish or grayish pultaceous stools, very acid in reaction, and often yeasty in odor, and foamy."[2]

---

2. Ashford: Oxford Loose Leaf Medicine, **5**:631.

4. The postmortem findings were not those which have been described as typical of sprue. There was no effacement of the crypts of Lieberkühn, no deformation of the tubules, no small mucous cysts, no atrophy of the muscle layer of the small intestine, no great thinning of the intestine, and no typical bottle-shaped ulcerations. Moreover, it is of some significance that, whereas the most intense changes in sprue occur in the duodenum and jejunum, the most marked postmortem changes in this case were referable to the ileum. Finally, no organisms, such as have been described by Ashford, were found.

It would seem that a definite clinical and pathologic syndrome with such an intangible etiologic background must have been previously recognized. Nevertheless, search of the literature has uncovered only one analogous case, reported by G. H. Whipple.[3] This case was characterized clinically by a gradual loss of weight and strength; stools consisting chiefly of neutral fat and fatty acids; indefinite abdominal signs, and a peculiar multiple arthritis. Considerable actone was found in the urine before death. The red blood cells averaged 2,000,000; the hemoglobins 53 per cent. Pathologically, the lesions of interest were found in the intestines and the lymphatics of drainage. The intestinal mucosa showed villi enlarged from deposits of masses of neutral fats and fatty acids in the lymph spaces, and an infiltration of the interglandular tissue by large mononuclear and polynuclear giant cells. The glands showed a similar deposition of fatty substances and a similar inflammatory infiltration.

In the occurrence of fatty stools, great loss of weight and strength, enlarged mesenteric lymph nodes containing fatty substances, tetany (in two), a terminal condition of acidosis (in two), and otherwise essentially normal postmortem findings, the cases here described are similar. On the other hand, none of the cases here described was characterized by arthritis, eosinophilia, fever, purpura or enlarged intestinal villi, as found in Whipples' case. In all essential characteristics, these all seem to belong definitely to one disease group.

Many features of the disease excited considerable interest, particularly the appearance of tetany in two of the cases. The low blood calcium is in accord with the findings of Howland and Marriott [4] in children. They found a uniformly low blood calcium, averaging 5 mg. per hundred cubic centimeters, in tetany, and in no other convulsive disorders. The abatement of the symptoms in the last case after calcium lactate was given by mouth is likewise similar to their experience. The

3. Whipple, G. H.: A Hitherto Undescribed Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic Tissues, Bull. Johns Hopkins Hosp. **18**:382 (Sept.) 1907.

4. Howland, J., and Marriott, W. M.: Quart. J. Med. **11**:289 (July) 1918.

normal phosphate content of the blood in the third case is also in accord with the frequent findings in the tetany of children.[5]

It would seem that the occurrence of tetany in two out of our three cases must be of more than passing significance, in view of the fact that thousands of instances of more severe acidosis constantly occur without producing such symptoms. The exact importance of the low calcium is not clear, for in the acidosis of nephritis the calcium is frequently reduced far more without the production of tetany, although the possibility of the occurrence of the latter is demonstrated by a recent instance in this hospital.

Tetany in adults, although unusual, is by no means rare. In this connection, the reports by Bassett Smith,[6] and by Barach and Murray [7] of two such cases associated with the gastro-intestinal disturbances of sprue, is interesting. The blood calcium in the latter case was 6.5 mg. per hundred cubic centimeters, the plasma carbon dioxid 57.6 per cent. by volume. The latter authors present the interesting speculation that since the absorption of calcium is effected in combination with fatty acids, and since the absorption of the latter vehicle is faulty in sprue, the low blood calcium is not altogether surprising.

Findlay and Sharpe [8] found a diminished absorption of fat in cases of adult tetany, but absolutely no deficiency in the ability to split fat. These results are similar to the observations made in Case 2.

The acidosis in two of the three cases here reported must have been referable directly to the malnutrition, and not to any nephritic factor, such as has been observed by Marriott and Howland in the acidosis of marasmus in children.[9] The normal nitrogenous constituents of the blood, the normal urinary findings, the normal phenolsulphonephthalein excretion, exclude any serious impairment of renal function.

In view of the marked undernutrition, the low temperature and the necessarily increased body surface in relation to the body weight, the metabolic rate in the third case was higher than has been expected. The marked secondary anemia may have been a stimulating factor; for it has been shown that the metabolic rate in secondary anemia tends to be increased, and it can be shown to fall after transfusion.[10]

---

5. Kramer, B.; Tisdall, F. F., and Howland, J.: Observations on Infantile Tetany, Am. J. Dis. Child. **22**:431 (Nov.) 1921.

6. Smith, Bassett: Case of Sprue Associated with Tetany, Lancet **1**:178 (Feb.) 1919.

7. Barach, A. L. ,and Murray, H. A., Jr.: Tetany in Case of Sprue, J. A. M. A. **74**:786 (March 20) 1920.

8. Findlay, L., and Sharpe, J. S.: Adult Tetany and Methylguanidin: a Metabolic Study, Quart. J. Med. **13**:433 (July) 1920.

9. Marriott, W. M., and Howland, J.: Phosphate Retention, Arch. Int. Med. **18**:708 (Nov.) 1916.

10. Tompkins, E. H.; Brittingham, H. H., and Drinker, C. K.: Basal Metabolism in Anemia, with Especial Reference to the Effect of Blood Transfusion on the Basal Metabolism in Pernicious Anemia, Arch. Int. Med. **23**:441 (April) 1919.

The exact significance of the megacolon in the third case is uncertain. Whether the condition was congenital or merely consequent to the atony of the intestinal musculature, it is impossible to state. The megacolon, the hypermotility, the dryness of the skin, raised the question whether a disturbance of the water metabolism was playing an important rôle. Certain features were not in accord with this conception. The urinary output was always maintained at a satisfactory level. To be sure, in certain diseased states, notably diabetes insipidus, desiccation of the tissues may exist coincidentally with a high urinary output. Pituitary extract in small doses was given to the third patient in an attempt to favor fluid retention in the tissues, but without any influence on the clinical course. If one may assume that the same physiologic factors operate in adults that Marriott has shown exist in children, the presence of an anhydremia in these cases is extremely improbable. In the first place, an anhydremia is accompanied by desiccation of the blood and profound renal damage. Schloss particularly has shown that the degree of desiccation of the blood is proportionate to the degree of renal damage. As previously stated, there was no evidence either during life or postmortem to indicate any serious impairment of renal function.

SUMMARY

Three cases are presented, which, because of certain features they share in common, suggest a possible clinical entity: The disease tended to occur in early middle life, with insidious onset, gradual downward progression over a period of one and a half to two years, finally terminating in death. The presenting symptoms were weakness, emaciation, on the average of three soft, semisolid, yellow bowel movements daily, with an excess of fat. Acidosis and tetany were noted in two cases. In the two cases tested, there was an absence of free hydrochloric acid in the gastric contents. Examination of the blood showed a secondary anemia of 2,500,000 to 3,000,000 per cubic millimeter, a color index of approximately 1, but no other indications of primary anemia. All of the special studies and tests were essentially negative.

Pathologically, the significant changes were confined to the intestines and to the mesenteric lymph nodes. In all three necropsies, only incidental changes were found elsewhere. The small intestine showed small granular elevations of the mucosa, usually gray in appearance. Microscopically, these elevations were found to consist of phagocytes containing ingested fat. The phagocytes were large and mononuclear, and contained a foamy reticulated cytoplasm. The mesenteric lymph nodes were noticeably enlarged and hyperplastic, and contained similar phagocytes, with ingested fat.

CHYLOUS AND PSEUDOCHYLOUS EFFUSIONS

A REPORT OF SEVEN CASES *

M. A. BLANKENHORN, M.D.

CLEVELAND

The purpose of this paper is to describe some unusual observations and discuss the probable cause of milky effusion in each case here recorded. Up to 1910, 242 cases had been reported, as shown in a summary by Wallis and Schölberg.[1] It is probable that many cases have not been published, for there is usually nothing to report save that milky fluids are present, and the milkiness is unexplained. Wallis and Schölberg found 81 cases due to tumors; 46 to infections, of which 33 were ascribed to tuberculosis; and 37 due to affections of the thoracic duct and lymphatics. Seventy-eight remained in a group of general diseases, 22 of which were specified further as nephritis, and 28 as cirrhosis of the liver. These figures are interesting as statistics, but they give milky effusions no diagnostic value, and not until there is definite information in terms of pathologic physiology and anatomy will any particular milky fluid be a helpful diagnostic sign.

Theories abound as to these fluids, as shown by the terminology in reports—chylous, chyliform, adipose and pseudochylous. In the American Medical Dictionary, chylous ascites is defined as "the presence of chyle in the peritoneal cavity due to rupture of a chyliferous vessel." Chyliform ascites is given as synonymous with chylous. Adipose ascites is "a variety characterized by a milky appearance of the contained fluid due to the presence of cells that have undergone fatty degeneraion." Pseudochylous is "ascites in which the contained fluid resembles chyle in appearance, but does not contain fatty matter." Of these terms, the only one that we find no fault with is "chylous," for it implies definite pathology and is well established. The term "adipose ascites" was never founded on fact and has no general use. "Chyliform" and "pseudochylous" are used indiscriminately to designate all milky fluids not definitely chylous, and against them I join the lists, believing that no one has found definitely milky fluids the turbidity of which was not due to the presence of emulsified fat derived from the chyle.

Observers have indeed found unusual substances in milky fluids, but there is as yet no certain demonstration that these unusual substances were the cause of turbidity. In two cases described by Lion,[2]

---

* From the department of medicine of Western Reserve University and Lakeside Hospital.

1. Wallis, R. T. M., and Schölberg, H. A.: Quart. J. Med., Oxford **4**:153, 1910-1911.

2. Lion, M. G.: Arch. de méd. exper. et d'anat. path. **5**:286, 1893.

glucoprotein was found. Taylor and Fawcett[3] found an unknown protein, and Joachim found a lecithin-globulin complex; but all of these observers used inadequate methods to exclude fat as the turbid agent, and assumed their respective proteins to be the only possible cause. If we agree, as many do, that fat is the cause of turbidity, there are still many obstacles in the way of a satisfactory classification of these fluids, especially on the basis of their various ingredients. These difficulties are seen in the attempt at classification made by Powell and Hartley.[4] These writers find eighteen points of distinction between chylous and pseudochylous, but in all except two instances the difference is a matter of degree, the chylous fluids being more concentrated than the pseudochylous. The remaining points deal with the unusual proteins mentioned above—mucinoids and lecithin-globulin. Classification must fail when there are variable factors which cannot be evaluated, such as the presence of inflammation with exudation, transudation of body fluids or alteration in food intake.

This paper was written on the premise that emulsified fat alone is the cause of milkiness, and it aims to point out in each case cited the mechanism whereby fat may appear in an effusion. Such a premise was established by an investigation into the nature of milky effusions, the details of which will be given in another paper. By proving that emulsified fat is the sole cause of milkiness in effusions, we have gone a long way in their classification, and may hope ultimately to make the finding of milky effusions a valuable diagnostic sign.

REPORT OF CASES

Case 1.—A white man, aged 40, admitted to hospital, Oct. 12, 1919, having been in four months previously with a diagnosis of mediastinal tumor, had signs of fluid in the right chest, with massive retrosternal dulness and tremendous obstruction of the veins of the neck. Thoracentesis, October 24, removed 1,268 c.c. of milky, slightly hemorrhagic fluid; October 25, 1,060 c.c. of similar fluid; November 11, 1,800 c.c., milky but more hemorrhagic; December 5, 1,000 c.c., milky with less hemorrhage, and Jan. 1, 1920, 1,400 c.c., very creamy with slight hemorrhage. During this time, the patient was receiving roentgen-ray treatment, and he became comfortable enough to be discharged. He was sent to Baltimore for radium treatment. At the present time, April, 1922, he shows no signs of tumor, and has had no treatment for one year.

The four specimens obtained were uniform, except in the amount of blood admixture. One specimen, the bloodiest of the four, developed a partial clot. The fluid reaction was alkaline; the specific gravity 1.017. There were 17,760 cells per cubic millimeter, 20 per cent. red blood cells and 80 per cent. leukocytes. Of the leukocytes, 90 per cent. were small lymphocytes. The cells all stained well, and showed no degeneration. Centrifugation threw down a mass of cells, as described above, and small clots. It also brought up a heavy creamy layer, which under the microscope showed coarse and fine spherical bodies, as well as microscopic granules. Prolonged centrifugation brought

3. Taylor, Frederick, and Fawcett, John: Tr. Clin. Soc., London **38**:169, 1905.

4. Powell and Hartley: Diseases of the Lungs, 1921.

no further change, nor did standing for a month or filtering through paper. Heat coagulation formed a very heavy clot without the addition of acid; with acid, clotting was complete and the fluid filtered clear. There was no reduction of Benedict's solution. Shaking with ether made very little change in the appearance of the fluid, but the ether on evaporation left a thick, yellow, greasy residue, which smelled like butter. This residue contained no crystals. It stained with sudan III and gave an acrolein reaction when heated.

Comment.—In this case, it is quite certain that a tumor had developed with subsequent rupture or possibly with actual ulceration of the thoracic duct. The fluid here obtained must have been chyle with an admixture of blood. The formation of the creamy layer on centrifugation or on standing, the large size of the fat droplets and the ease of extracting with ether indicate a coarse emulsion of the fat in generous amounts as the cause of turbidity. Such an emulsion must have been poured directly from chyliferous vessels into the pleural cavity without any process of filtration. Before centrifugation, this fluid was clearly chylous in the accepted term, but the important fact must be noted that, when coarse fat particles were removed by centrifugation, the remaining chylous fluid could not be distinguished from the so-called pseudochylous.

CASE 2.—A white woman, aged 42, was admitted Feb. 2, 1921, with a diagnosis of metastatic carcinoma of the abdomen and thorax, following a breast amputation two years previously, with later axillary dissection for carcinoma. February 25, a liter of bloody fluid was removed from the left pleural cavity; May 5, the left chest was again aspirated, and 1,000 c.c. of fluid removed; May 6, abdominal paracentesis was performed and 1,800 c.c. removed; and, June 4, 1,200 c.c. was removed from the abdomen. June 5, the patient was discharged to her home, where she required numerous tappings, and died a few months later. There was no necropsy.

In this case, the fluid was alkaline in reaction and had no odor. It was of a brownish-yellow, turbid appearance, and had a specific gravity of 1.020. Centrifugation threw down many cells and brought up a small creamy layer, partly clearing the fluid and greatly diminishing the red-brown color. The cells were largely red cells, but there were 260 white cells per cubic millimeter, which stained very well, showing no gross degeneration or vacuolization. Small lymphocytes predominated, but a few large mononuclear cells suggested carcinoma. Only minute spherical bodies could be seen, but there were many ultramicroscopic particles, with rapid brownian movement. Filtering through paper made no change, but filtering through porcelain left a perfectly clear fluid, faintly brownish red. Boiling with weak acetic acid formed a heavy coagulum, which, when filtered off, left a clear brown fluid. Salting out with ammonium sulphate, ⅛ saturation, gave no appreciable change; ¼ saturation gave a slight precipitate and partial clearing; ½ saturation gave a heavy precipitate and complete clearing, after which full saturation again threw down a heavy precipitate. No protein was detected after heat coagulation with acid, and the biuret test showed no peptone. There was no glucoprotein, for after heat coagulation there was no reduction of Fehling's solution before or after hydrolysis of the filtrate. Shaking with ether did not clear the fluid, but a small amount of fat was recovered. Prolonged extraction of the dried residue removed 0.129 gm. of fat per hundred cubic centimeters, and a trace of lecithin. Filtering through porcelain diminished the total nitrogen from 0.770 to 0.560 gm. per hundred cubic centimeters, and diminished the fat from 0.129 to 0.019 gm. per hundred cubic centimeters. Amylolytic ferments were not found.

Comment.—The fluid in this case, after the cells had been removed by centrifugation, conformed to the usual description of pseudochylous fluids, and we may assume that the turbidity was due to fat, for no other substance, particularly no lecithin-globulin complex, no nucleoprotein nor mucinoid substance could be found; and with porcelain-filtration there was equal diminution

of turbidity and of fat. Fat here could not be due to degeneration of cells, for the fluid reaccumulated very rapidly; furthermore, no degenerated cells could be found. It is most plausible to assume that, in this patient, in whom extensive metastases were demonstrated in the abdomen and thorax, there was actual obstruction of chyliferous ducts by tumor masses, and the chyle escaped by a process of filtration.

Case 3.—A white woman, aged 29, admitted, August 23, 1915, and discharged, May 7, 1916, had been sick ten days, and the intestinal hemorrhages, leukopenia and a positive Widal reaction indicated that she was suffering from typhoid. Convalescence was very slow, and in the third month, she had a ptosis of the left eyelid and a peripheral neuritis of both legs. The heart at this time was slightly enlarged, and the pulse was frequently as high as 140, although the temperature was normal. In this period, she was very anemic, having but 2,736,000 red cells and a hemoglobin of 60 per cent. A lumbar puncture was made, and a normal cell count was reported. The neuritis was explained as posttyphoid intoxication.

November 29, while still quite anemic and with troublesome peripheral neuritis in the legs, she developed effusion into the abdomen and both sides of the chest, and a general anasarca, although she remained afebrile and had no leukocytosis. At no time during the course of the long convalescence was anything discovered to explain the ascites, much less the milky nature of the fluid. During convalescence, she developed a respiratory infection diagnosed as influenza, an acute streptococcus tonsillitis and a double otitis media; but no evidence was adduced to indicate a generalized infection or tuberculosis, which might have caused peritonitis and pleurisy, thereby obstructing chyliferous vessels. In default of further information, the effusion must be regarded as a sequel of typhoid fever.

Fifty cubic centimeters of abdominal fluid was obtained. This was of a bluish opalescence, had no odor, and was unaffected by centrifugation, settling or long standing. When shaken with ether, it was unchanged in appearance, and the ether contained no fat. It had a specific gravity of 1.008, and an albumin content of 0.2 gm. per hundred cubic centimeters. It contained 120 cells per cubic millimeter, largely mononuclears.

Fifty cubic centimeters of thoracic fluid was obtained, identical with the abdominal in appearance and character, excepting that the specific gravity was 1.005 and the albumin content 0.4 gm. per hundred cubic centimeters.

Comment.—The meager data obtained in this case deserve little discussion, but one may say that the general anasarca, seen in the absence of nephritis and cardiac disease, suggests edema due to starvation or anemia. The very low specific gravity, the very low albumin content and probably low fat content suggest that this accumulation of fluid was due to a filtration through membrane made unduly permeable by starvation or prolonged infection. This filtration of a suspension of fat could have come by way of the chyliferous ducts or even from the blood stream. The patient was very anemic, and Bloor[5] has pointed out that in the anemias there is an increase in the lipoids of blood serum. A milky effusion direct from blood capillaries must be considered as a possible cause, and it is regretted that more complete observations were not made as to the nature of the blood serum.

Case 4.—A white woman, aged 33, admitted, October 26, 1920, complaining of nephritis and diarrhea, with no previous indisposition except from what was said to be a tonsillitis, had been suffering from the present illness for eleven weeks, it appearing first as a swelling of the feet, which progressed in a few days to a general anasarca but with no demonstrable cardiac stasis. The blood pressure was 110, systolic, 65, diastolic; but prior to admission, it had been found by her physician to be much elevated. The urine was scanty and of high specific gravity, with much albumin and many casts. Paracentesis was

5. Bloor, W. R., and MacPherson, D. J.: J. Biol. Chem. **31**:79 (July) 1917.

performed, and 700 c.c. of milky fluid was removed from the left chest. One week later, the right chest was tapped, and 800 c.c. of milky fluid was removed, after which 3 liters of similar fluid was removed from the abdomen. With the thorax and abdomen quite dry, no disease of the pleura could be defined, and nothing unusual could be discovered by palpation about the abdomen. Six days later, both sides of the chest were tapped, and 800 c.c. was removed from the left and 500 from the right. The fluid resembled that previously obtained.

The nephritis became rapidly worse, resulting in death within two weeks. Permission for necropsy was not granted.

The abdominal fluid contained no amylolytic ferment, no cholesterol, no lecithin, no mucinoid substance and no glucoprotein. There was no peptone by biuret reaction on a fresh specimen, but when the specimen had stood a month or more, a peptone test was positive. Half saturation with ammonium sulphate and boiling with weak acetic acid cleared the fluid. Centrifugation brought up no creamy layer, and after long standing there was none. Filtering through porcelain reduced the fat from 0.020 to 0.0073 gm. per hundred cubic centimeters and gave a clear filtrate. Shaking with ether caused no clearing and the ether contained no fat, but shaking with a mixture of alcohol and ether almost completely cleared the fluid until coagulation of protein occurred. Prolonged extraction of the dried residue with ether yielded about 0.02 gm. of fat per

TABLE 1.—*Analyses of Fluids in Case 4*

	Fluid from		
	Abdomen	Left Side of Chest	Right Side of Chest
Specific gravity	1.010	1.010	1.010
Total nitrogen *	0.140	0.140	0.143
Sugar	0.075	0.110	0.100
Urea	0.082	0.089	0.084
Chlorids	0.750	0.630	0.625
Fat	0.02	0.020	0.018
Total solids	1.09	1.236	1.188

* All solids are stated in grams per hundred cubic centimeters.

hundred cubic centimeters, and in this there was no cholesterol or lecithin. The centrifuged residue from all these fluids showed only a few mononuclear cells, which stained well. There was no cell débris.

Comment.—The fluids obtained from the patient conform absolutely to the pseudochylous type, but other than emulsified fat no substance was found that could cause turbidity, especially no lecithin, no cholesterol, no glucoprotein and no mucin. It might have been doubted whether 0.02 gm. of emulsified fat per hundred cubic centimeters is sufficient to cause such turbidity, but proof that it can do so will be presented in another paper. How this emulsified fat escaped into the abdomen and chest must remain a matter of conjecture. There are two sources for such fat—the thoracic duct and its branches, and the blood itself. In nephritis, a condition known as lipemia has been described, in which the blood serum becomes milky, and in this case there may have been a transudation of milky serum without leakage of chyle. Such an explanation is suggested by the uniformity of the fluids from the abdomen and both sides of the thorax. No observation on the fat content or the appearance of the blood was made in this case.

CASE 5.—A colored man, aged 24, who was transferred from the Cleveland City Hospital by the courtesy of Dr. Scott, with a diagnosis of chronic nephritis with chylous ascites, had had acute nephritis eight months previously in a Southern hospital, and milky fluid had four times been evacuated from

the abdomen. Admission to City Hospital was sought because of an exaggeration of the chronic edematous state that had persisted from the onset of the disease.

When he was admitted to Lakeside Hospital, the blood pressure was 130, systolic, 90, diastolic, and the urinary output was about a liter a day, with a specific gravity of 1.020, a large amount of albumin and no renal elements. He eliminated 45 per cent. of phenolsulphonephthalein in two hours, and by the two-hour specific gravity test, he had a maximum variation of 10 points, the highest being 1.025 and the lowest 1.015. He was distinctly anemic, having a red blood count of 1,350,000, and a hemoglobin of 50 per cent. The abdomen was tapped on account of extreme distention, three days after admission, and 3,800 c.c. of milky fluid was evacuated. He was placed on a salt-free, low-protein diet, and kept in bed, and in spite of the long duration of his illness and its apparent severity, he made a good recovery and was discharged within five weeks very much improved. It was impossible to make any addition to the original diagnosis, although tuberculous peritonitis was considered.

Since discharge, one year ago, this patient has been under observation in the outpatient clinic, having reported frequently, once to be tapped. His blood pressure is sometimes as high as 170, systolic, 120, diastolic, and he has more albumin in the urine than when discharged from the hospital. Hyaline and granular casts also have appeared. On his last visit, four months after being discharged, he had a phenolsulphonephthalein output of 47 per cent. in two hours, and the specific gravity of the night urine was 1.016, and of the morning

TABLE 2.—*Analysis of Fluid from Abdomen (Case 5)*

Specific gravity, 1.010	Gm. per 100 C.c.
Total nitrogen	0.505
Sugar	0.130
Urea	0.060
Chlorids	0.750
Fat	0.018
Solids	1.575

specimen, 1.009. He remains free from edema and is able to work as a waiter, but continues with marked albuminuria and high blood pressure, due to chronic nephritis.

The fluid contained amylolytic ferment as well as dextrose. The biuret gave no peptone reaction when the fluid was freshly drawn, but about a month later a positive peptone reaction occurred. There was no cholesterol, no lecithin, no mucinoid substance and no glucoproteid. Filtering through porcelain cleared the fluid, as did ½ saturation with ammonium sulphate and boiling with acetic acid. Centrifugation brought up a creamy layer, and long standing developed a similar layer. Shaking with ether caused no clearing but brought up a faint amount of grease, which stained black with osmic acid. Shaking with a mixture of ether and alcohol momentarily cleared the fluid until coagulation of protein occurred. Extraction of a dried residue yielded 0.018 gm. of fat per hundred cubic centimeters, but extraction of the dried residue of a clear porcelain filtrate yielded only 0.0046 gm. of fat per hundred cubic centimeters. The fluid was distinctly more turbid than that from Case 4. There were 130 cells per cubic millimeter, 50 per cent. being lymphocytes; all stained well, and there was no cell débris.

Comment.—This is another definitely pseudochylous fluid, coming from a patient with severe nephritis and anemia, but with no evidence of disease of the thoracic duct or its contributaries. As to the mechanism of milky ascites, what was said in the discussion of Case 4 applies here, except that in this instance the oxalated plasma was twice examined and found to be perfectly clear. Under the microscope the ascitic fluid showed a few recognizable fat droplets, but although the fat content was the same as in Case 4, unlike the

other this fluid produced a faint creamy layer when centrifugated. From this, it is apparent that turbidity is not an index of fat content, nor is the size of fat particles dependent on total fat content.

Case 6.—A man, aged 32, admitted Nov. 29, 1920, complaining of edema of the legs, shortness of breath and swelling of the abdomen, had been wounded in battle, Sept. 28, 1918, being shot by a machine gun in the thigh. After about six weeks, he was found to have an enlarged heart with signs of aortic regurgitation and arteriovenous aneurysm in the thigh. Before admission to Lakeside Hospital, he was tapped about forty times for large amounts, and according to his own story the fluid at times was perfectly clear and at other times distinctly turbid, but never milky. When he was tapped at Lakeside Hospital, the 11 liters of fluid recovered was amber, and distinctly milky.

He was operated on, and the anastomosis between artery and vein was closed off. Immediately thereafter, the blood pressure, which had been 115 systolic, 65 diastolic, became 145 systolic, 95 diastolic. After a convalescence of four months, during which time he had no reaccumulation of fluid, he was entirely free from disability, and he now is practically well. The change in blood pressure at the time of operation as a result of stopping the leakage from artery into vein can be taken as evidence that blood pressure in the vena cava had been elevated by arterial leakage, and was diminished by the repair. It was seen after operation that pulsations in the jugular vein ceased.

The abdominal fluid was pale yellow and milky, with a fragile clot that settled in the flask. The specific gravity was 1.008.

Table 3.—*Analysis of Fluid in Case 6*

	Gm. per 100 C.c.
Total nitrogen	0.170
Sugar	0.060
Urea	0.086
Chlorids	0.680
Fat	0.028
Solids	1.028

This fluid contained amylolytic ferment as well as sugar. The biuret on the fresh specimen gave no peptone reaction, but after a time a peptone reaction developed. There was no cholesterol, lecithin, mucinoid substance or glucoproteid. Filtering through porcelain cleared the fluid, and so did heat coagulation with acetic acid and ½ saturation with ammonium sulphate. Centrifugation brought up a faint creamy layer, as did standing. Shaking with ether caused no clearing, but a small amount of fat was recovered and the dry residue of the whole fluid yielded 0.028 gm. of fat per hundred cubic centimeters. Under the microscope, fat droplets were visible. There were 125 cells per cubic millimeter, of which 75 per cent were mononuclear.

Comment.—This fluid is also of the pseudochylous variety, of low specific gravity, and low protein and fat content. There is adequate reason to suppose there was obstruction to the drainage of chyle into the subclavian vein, for the blood pressure in the cava system was greatly elevated by the leakage of a large volume of blood into the femoral vein at arterial pressure. The theory is offered that, as a consequence of high intravenous pressure, there was back pressure in the lactiferous vessels, with transudation of much diluted and filtered chyle. The blood serum of this patient was perfectly clear, so that it is unlikely that the turbid effusion was from this source.

Case 7.—A white man, who had been in Lakeside Hospital from June 30 to July 30, 1920, was discharged with a diagnosis of parenchymatous nephritis. The urine at that time had a high specific gravity and contained large amounts of albumin and many granular casts; the phenolsulphonephthalein output was 60 per cent., and the blood pressure was never elevated, being frequently below 100.

He was readmitted, August 21, and continued in the hospital until his death, Oct. 8, 1921. The final diagnosis was: peritonitis fibrosus, ascites chylosus, chronic parenchymatous nephritis and chronic interstitial hepatitis. During his long stay in hospital, the nephritis made definite progress, so that the urine was even more diminished in volume and contained larger and larger amounts of albumin up to 10 gm. per liter. The lowest phenolsulphonephthalein output was 55 per cent. The specific gravity of the urine was always high, with a total volume frequently of no more than 400 c.c. He had no fever. The blood nitrogen was never higher than 90 mg. per hundred cubic centimeters. For a long time, his appetite was good, and his strength permitted him to walk about the ward. He gradually deteriorated until he was no longer able to be out of bed, and he refused to take food. Toward his latter days, he became very edematous and complained of pain in the upper abdomen. Before death, a roentgen-ray examination with pneumoperitoneum was made, which made him very uncomfortable. A diagnosis of chronic adhesive peritonitis with cirrhosis of the liver was made from the plates.

During the second admission, the abdomen was tapped thirty-six times at intervals varying from three to fourteen days, the average being eleven days. The length of time was dependent on the fluid intake and the physical activity of the patient. Rest in bed and restricted intake prolonged the intervals. He had no medication except an occasional cathartic, sedatives when he complained of sleeplessness, and a short course of antisyphilitic treatment with mercury

TABLE 4.—*Analyses of Specimens in Case 7*

	Greatest	Least
Specific gravity	1.012	1.006
Total nitrogen (gm. per 100 c.c.)	0.490	0.140
Sugar (gm. per 100 c.c.)	0.150	0.000
Urea (gm. per 100 c.c.)	0.100	0.000
Chlorids (gm. per 100 c.c.)	0.750	0.200
Fat (gm. per 100 c.c.)	0.201	0.090
Total solids (gm. per 100 c.c.)	2.9	1.8

and potassium iodid, which had to be stopped on account of increasing albuminuria. The blood Wassermann reaction had been negative.

On one occasion, by feeding a diet rich in butter and cream, the fat content of the fluid was increased from 0.128 gm. to 0.201 gm. per hundred cubic centimeters, following which it dropped below its former level. As the patient refused the diet, the experiment could not be repeated.

Blood fat, estimated at various times on whole blood, was from 123 to 135 mg. per hundred cubic centimeters. At no time was the serum or oxalated plasma abnormally turbid.

Chemical analysis was made of many of the thirty-six specimens, the extreme results of which are given in Table 4. The average of all analyses is approximately the average of these extremes.

These specimens all contained amylolytic ferments when tested, and sugar was never absent. The biuret test on freshly drawn specimens was negative, but after they stood a month or more it was uniformly positive for peptone. In the ether extract, traces of cholesterol and lecithin were occasionally present, but not necessarily at the same time. In one specimen, there was a substance—probably glucoprotein—which was precipitated by alcohol after all heat-coagulated protein had been removed, and which after hydrolysis with hydrochloric acid reduced Fehling's solution. Its presence could be easily demonstrated in one specimen, but never in any previous or subsequent tappings.

Filtering removed on one occasion 93 per cent. of fat and 20 per cent. of protein; on another occasion, 90 per cent. of fat and 9 per cent. of protein. Heat-coagulation with weak acetic acid cleared these fluids, as did ½ saturation with ammonium sulphate. Centrifugation or long standing always brought

up a small creamy layer. Except for this creamy layer and a faint white sedimentation, some of the specimens remained unchanged after more than eighteen months at room temperature in loosely stoppered flasks. Shaking with ether, if prolonged an hour or more in a machine, developed a gelatinous gummy mass, which was difficult to separate from the extracting ether. This mass was always present unless the fluids became acid from putrefaction or by direct addition of acid. Such extraction with ether seldom removed more than 0.030 mg. of fat per hundred cubic centimeters, and did not materially clear the fluid. Extraction of the dried residue prolonged for from forty to sixty hours in a Soxhlet apparatus removed all extractable fat, including occasional traces of lecithin and cholesterol. Shaking with a mixture of ether and alcohol cleared all turbidity until coagulation of protein occurred. In fresh specimens, the microscope revealed from 120 to 300 cells per cubic millimeter, largely small, readily stainable lymphocytes. Small oil droplets were seen and many ultramicroscopic bodies.

This man died, and necropsy was performed two hours after death. Following is an abstract of the report made by the pathologist, Dr. B. S. Kline:

Except for edema of the lower extremities the body showed nothing externally. On opening the abdomen, the parietal peritoneum was found everywhere to be strikingly thickened, being covered with a pearly white membrane, a millimeter in thickness. In places, injected vessels were visible on the surface. Two and one half liters of milky fluid were evacuated. A portion of the transverse colon and stomach were walled off from the peritoneal cavity by a membrane similar to and continuous with the parietal peritoneum, and a similar membrane extended from the right lobe of the liver to the abdominal wall.

On opening the thorax, the right pleural cavity contained 50 c.c. of slightly turbid, yellowish fluid. The left contained 1¼ liters of fluid similar to that in the abdomen. There was a similar pearly white membrane over the visceral and parietal pleurae on the left side, but in places it was diffusely injected. The pericardial chamber contained its normal amount of fluid. The liver weighed 1.050 gm. It was increased in consistency, and on section portions of the thickened capsule could be seen penetrating the substance of the liver. The vena cava and large branches, as well as the thoracic duct, which was dissected throughout, showed no abnormality.

Histologic examination of the kidneys showed the usual picture of chronic parenchymatous nephritis, with much fatty degeneration but no fat infiltration.

Section of the small intestine showed an unusual gross appearance. The striking thing was the marked thickening of the serosa. The portion toward the muscle was composed of loose areolar tissue, the cells separated by a considerable amount of amorphous pink-stained material. Scattered throughout, there were fairly numerous wandering cells, the majority mononuclear, many of these polyblasts or endotheliocytes. Numerous eosinophils were also present. The outer coats were composed of layers of fibroblasts and newly formed blood vessels, with cells separated by loose, amorphous, pink-stained material. In some areas, there were small mononuclear round cells, and the outermost portion of the wall was partly composed of a thin layer of fibrin, invaded by fibroblasts, or entirely replaced by them. In places, in the depth of the granulation tissue, there were amorphous pink-stained masses suggesting fibrin. In the granulation tissue, no lymphatics were observed, and those in the muscular layer and mucosa were not unduly conspicuous. The impression was gained that the process consisted of repeated depositions and organizations of fibrinous exudate.

Section of the liver and spleen showed this same change within the serosa, as well as atrophy of the liver tissue, but no increase of stroma within the liver lobules.

Section of the parietal pleura showed a thick layer of granulation tissue made up of fibroblasts, sprouting capillaries with prominent endothelium and

wandering cells (small mononuclears, plasma cells and endotheliocytes in about equal numbers). This section gave the impression that the process was a low-grade inflammation, with deposition of fibrinous exudate followed by organization.

Section of the mesenteric lymph gland showed the sinuses filled with large endotheliocytes and a considerable amount of amorphous, pink-stained material. In areas, there were numerous eosinophils and an increase in the stroma of the gland, especially about the blood vessels.

The complete pathologic diagnosis was: old tuberculous bronchial and mesenteric lymph nodes; encapsulated tubercles in the left upper lobes; chronic diffuse peritonitis with chylous ascites; chronic diffuse pleurisy with chylous effusion; capsular cirrhosis of the liver; beginning involution of the pancreas; chronic parenchymatous nephritis; atrophy and replacement fibrosis of the testes; complete inguinal hernia, right; old fracture of the left tibia. Probable cause of death was: chronic peritonitis with chylous ascites; chronic pleurisy, left, with effusion.

Comment.—This fluid from its chemical and physical nature must be classed as pseudochylous. Furthermore, although the thoracic duct and its coarser branches, as well as the vena cava superior, were demonstrated free from obstruction, the milky appearance can be shown to have been due to emulsified fat. Evidence to this effect is contained within this report, but the major proof will be presented in another paper. Presumptive evidence is seen in the fact that the fat content of this fluid was increased by fat feeding—the so-called Strauss[6] sign—which points both to fat as the cause of milkiness and to absorbed fat as the source. Fat was present in the form of emulsion, the separate particles of which varied from microscopic globules to ultramicroscopic particles that would pass an ultrafilter.

How emulsified fat might occur in this case is not clearly demonstrated by necropsy, but adequate cause is at hand in the extensive fibrosis of intestines and mesentery. A second possibility deserving discussion is the formation of fat by degeneration of fixed or exuded cells. The extreme rapidity with which the fluids formed in this case—11 liters in three days—speaks convincingly against this explanation. Furthermore, no such degenerated cells could be found free in the fluid or in the walls of the cavity generating the fluid. Further still, fat formed by degeneration of cells and tissues is disposed in coarse emulsions, often in coarse globules.

A third possibility is that a lipemic serum could have transuded from blood capillaries. This theory is incapable of being proved or disproved. In this instance, the observed serum was never of the same appearance as the fluids in question. One argument in favor of this origin is the surprisingly close correspondence between the amounts of blood fat and effusion fat, but against this is the wide disparity in the amounts of serum protein and effusion protein; for it is difficult to imagine a filter allowing all the fat to pass but withholding nine-tenths of the protein. The very low fat and protein contents are more in harmony with the first theory, that filtration from lactiferous vessels was the mechanism of producing this milky effusion. The extensive fibrosis of the intestine and mesentery was quite sufficient to produce stasis at the very origin in chyliferous vessels of small dimensions.

In the chemical examination of the fluids described in connection with these cases, sugar was estimated by the Lewis-Benedict method; urea by urease and aeration; chlorids by the method of McLean, Van Slyke and Donley; cholesterol by that of Bloor, followed by the Liebermann-Burchard test; lecithin by acetone precipitation, and phosphorus by the molybdate test. Fat extractions were made with

6. Strauss, M. I: Arch. de physiol. norm. et path. **18**:367, 1886.

petroleum ether, but on account of the difficulty in obtaining petroleum ether with absolutely no nonvolatile residue, sulphuric ether was used when minute amounts of fat were dealt with.

Most of the routine procedures were carried out by Miss Ruth Trump, chemical technician in the medical research laboratory of Lakeside Hospital.

SUMMARY AND CONCLUSIONS

Seven cases are recorded, in all of which milky fluids were found. In one case, in which the patient had a tumor of the mediastinum, the fluid contained large amounts of fat in coarse and fine emulsion. This fluid can well be called chylous. In the remaining six cases, in all of which the patients were known to have lesions capable of effusion from chyliferous or blood vessels, the fluids contained smaller amounts of fat, in very fine emulsion; these fluids might be classed as pseudochylous, but the only difference between them and the first fluid is that they lacked large fat particles.

The terms "pseudochylous" and "chyliform" are descriptive, and imply much that is not true and had better be discarded.

The term "chylous" is accurate and general enough to designate all milky effusions save those that can be shown to originate from lipemic blood.

THE CAUSES OF TURBIDITY IN MILKY ASCITIC FLUIDS*

M. A. BLANKENHORN, M.D.

CLEVELAND

In a companion paper, in which I reported seven cases of milky effusion and described the so-called pseudochylous fluid from each, it was pointed out that there was disagreement as to the cause of the turbidity of such fluids, and as a consequence much confusion among the descriptive terms applied. Some writers hold that emulsified fat is the cause; others, finding very little fat, are unwilling to ascribe turbidity to amounts so insignificant; and still others, finding no fat, ascribe turbidity to an unknown protein or some uncommon substance, such as glucoprotein, mucinoids, or a lecithin-globulin complex. The present work was undertaken with the hope of throwing further light on the subject by investigation into the nature of the turbidity in five of seven fluids described in the previous paper. The results were clear-cut. Emulsified fat was proved in all five cases to be the cause of turbidity.

This finding is in disagreement with that of observers who have found emulsified fat in these fluids but in amounts so small that they considered it inadequate for turbidity. How much fat is necessary for turbidity is a matter often discussed, but the fineness of its division is seldom considered. This investigation deals critically with that point, but credit for priority must be given to Gandin,[1] who made a similar investigation and came to the conclusion that small amounts of fat cause turbidity. The conclusions of this paper are discordant also with those of investigators who find no fat, and it will be shown that their methods do not rule out the presence of fat. Our conclusions are further in disagreement with those ascribing turbidity to proteins, because on removing proteins, principally globulin, turbidity was dispelled; and it will be shown here that the methods used to remove proteins also remove suspended fat. It is therefore fallacious to ascribe turbidity to protein on that evidence.

In this investigation, emulsified fat was found in every specimen. Of the other substances supposed to cause turbidity, the only one found in any notable amounts was glucoprotein, which was present in the twenty-sixth specimen from Case 7, but in no other. Small amounts of lecithin and cholesterol were found, but nothing resembling mucin.

---

* From the department of medicine of Western Reserve University and Lakeside Hospital.

1. Gandin, S.: Ergebnisse der innern Medizin und Kinderheilkunde, Berlin, **22**:227, 1913.

In order to determine the cause of turbidity, the following plan was followed.

A. Microscopic examination.
B. Separation of the turbid substance by:
   1. Filtration.
   2. Sedimentation.
   3. Heat coagulation.
   4. Salting out.
   5. Mutual precipitation.
   6. Extraction.
   7. Freezing.
   8. Peptization.
   9. Electrolysis.
   10. Dialysis.
C. Synthesis of turbid fluids by:
   1. Operation on the thoracic duct of dogs.
   2. Homogenization of oil, water, protein and salt mixtures.
   3. Homogenization of oil-water mixtures.

Of these various lines of approach, synthesis alone was entirely successful and decisive. Separation by peptization, electrolysis, extraction, freezing or filtration was successful and corroborative in about the order given. Separation by salting out, mutual precipitation, sedimentation and heat coagulation was successful, but the results were open to contradictory interpretations, though in the main reconcilable throughout. Microscopic examination was merely corroborative, and dialysis was unsuccessful.

FILTRATION

Filtration was first tried. It was hoped by this means to isolate the substance causing turbidity, and thereby allow identification by chemical examination. Filtering through paper removed nothing, and Mandler filters accumulated no collectable filtrate. When very fine Mandler filters were used, a distinct clearing was noted, but no diatomecious filter produced complete clearing. This was determined by reading print through tubes of equal diameter and comparing the clearness of the view through the filtered with that through the unfiltered. When coarse Mandler filters were used, there was less clearing.

A Pasteur-Chamberland filter cleared the fluid completely, leaving a straw-colored, limpid filtrate, but the process was always slow and difficult, frequently impossible even with a pressure of 70 pounds, after a certain volume had passed. Several candles, after repeated use and clearing with alkali, became more permeable, thus allowing a filtrate to come through rapidly, but with definite milkiness.

Before filtration, these fluids contained from 19 to 200 mg. of extractable fat per hundred cubic centimeters. The filtrates when clear contained from 5 to 19 mg. of extractable fat per hundred cubic

centimeters. The unfilterable residue was collected with much difficulty and uncertainty as to amount, but by reversing the direction of flow, a small amount could sometimes be washed back. This contained fat and protein in variable amounts and varying proportion; in general, the longer the filtration, the greater the relative amount of protein. It was apparent at once that the residue could not be taken as the isolated and uncontaminated milky substance, for the longer filtration went on, the less permeable became the filter, until ultimately not even water passed through. A certain amount of protein could be further removed from the residue on the filter by washing through with large volumes of saline followed by water, but prolonged washing never produced a residue free from protein. On the other hand, long washing compressed the mass into a greasy scum, which was removed from the filter with much difficulty.

When filtrates were perfectly limpid, the average of five filtrations withheld 94.3 per cent. of all fat and 18 per cent. of all protein. When filtrates were more turbid, more fat was present. Graduated filtration, going on to so-called ultrafiltration, removed more and more fat, and at the same time the filtrates became less and less milky, but always an extremely small amount of fat continued to go through. In one instance, 19 mg. per hundred cubic centimeters passed the filter, and the filtrate appeared clear. This at first sight seems inconsistent, for two of the milky fluids, Nos. IV and V of our previous report, contained just that amount. But it must be recognized that fat in particles smaller than the wave length of light gives no milkiness; and further that clearness is a relative condition liable to be misjudged by ordinary observation.

Filtering through fresh frog skin with a method devised by Sollmann partly cleared the fluid, giving a milky filtrate and very cloudy residue. Twenty-five cubic centimeters of a fluid containing 20 mg. of fat and no protein was filtered at about 30 cm. of water pressure. In the 5 c.c. of residue, there was 11 mg. of fat and in the 20 c.c. of filtrate there was 9 mg., so that 45 per cent. had passed through. A similar membrane employed in the filtering of dilute ox serum at the same pressure allowed 66 per cent. of protein to pass. These results by Sollmann's method show that (1) finely suspended fat can pass a vital membrane; (2) protein passes better than fat, and the two substances can be partly separated; and (3) turbidity of these mixtures diminishes with fat content rather than with protein content.

By filtering pseudochylous fluids, the turbid substance can be removed from the suspending medium, but it is not isolated in pure form. Protein and fat are found both in the residue and in the filtrate, but fat is concentrated in the residue and turbidity is confined to it. Filtering through vital membranes allows more fat and a turbid filtrate

to pass. We can therefore conclude that fat particles are present in variable size; some are small enough to pass a porcelain filter and cause no turbidity, but mostly they are too large to pass, and do cause turbidity.

MICROSCOPIC EXAMINATION

Microscopic examination was undertaken to identify the turbid substance in situ. When the highest power oil immersion was used, the whole fluid was uniformly opaque, the field being composed of minute points with rapid brownian movement, with a few definitely spherical bodies. A filtrate when clear showed no particles, but the residue showed clumped-up bodies too small to be defined, among which were numerous globules. After long sedimentation or centrifuging, a thin filmy cream came up, composed principally of spherical forms, and the middle portion thus centrifuged showed no spherical forms, but granules with brownian movement. There was no sediment until the fluids had stood several months and then very little in a liter flask, and the body of the fluid was in no degree cleared.

From this it is apparent that these fluids contain particles in suspension as a dispersoid, some large enough to be recognized as definitely spherical, others too small to be defined. The spherical forms were never larger than one-fourth the diameter of a red cell; most of them were smaller, but no one size seemed to predominate. When filtration had cleared the fluid of milkiness, these suspended particles had disappeared.

SEDIMENTATION

Sedimentation was expected to isolate or at least concentrate the turbid substance. After standing a few days, the surface of these fluids all showed a more or less delicate film of bluish white, a creamy pellicle. Vigorous centrifuging—several hours at 2,300 per minute—produced the same effect. This pellicle could be made to disappear into the underlying fluid by very little shaking. When removed by a pipet, it could be freely suspended in distilled water or saline and again centrifuged out; and the natural pellicle formed by long standing behaved in the same manner. After the entire pellicle was removed, no amount of centrifuging could form another, not even after the addition of cane sugar sufficient to raise the specific gravity to 1.060 or salt to bring it to 1.080. The sediment seen after these fluids had been standing six months or more could be resuspended by shaking, and except for that part which was definitely flocculent or threadlike, it was a long time resettling.

From the bottom of a 2-liter flask that had stood sixteen months uncontaminated, a small amount of sediment was removed by pipetting.

This sediment was largely composed of needle crystals, single or in rosette clusters. The clusters were about 15 microns in diameter, and the crystals were about 7 microns long. This residue was insoluble in dilute alkali, acid, alcohol or ether. It was then tested for tyrosin and ammonium urate, and neither was found, but small amounts of an ether soluble substance was extracted, which gave reactions for cholesterol and lecithin.

From sedimentation of these fluids, it is shown that spherical bodies of appreciable size rise to the top after long centrifuging, making the top more turbid, but the bulk of dispersoid is composed of particles so small that physical forces, probably surface tension and surface charge, overcome sedimentation.

HEAT COAGULATION

Heat coagulation was employed to remove the greater part of the protein, leaving other substances in solution or suspension. Boiling produced no immediate change except in No. IV, which had an uncommonly large amount of protein, but on standing a few hours all showed more or less sediment and no clearing. Heating and acidulation formed a flocculent precipitate, which if undisturbed settled out, part going up and part becoming sediment, leaving a clear liquid. This coagulum from heating and acidulation when dried and extracted contained all the fat originally contained in the fluid. From this procedure, it is seen that heat coagulation of protein removes fat as well as protein, just as egg clears coffee. The clear filtrate from filtration through porcelain when heated produced an opalescence resembling that of the unfiltered fluid, but this milky fluid on standing under sterile conditions formed a generous sediment and eventually cleared again.

SALTING OUT

Salting out was employed to remove and isolate proteins. Diluting with 19 volumes of water at p_H 7 formed, after twenty-four hours, a faintly granular precipitate, which required several days for complete sedimentation. After sedimentation the fluid was still quite turbid, although the milkiness was much dissipated by the original diluting process. The collected precipitate when redissolved by adding crystals of salt did not make a perfectly clear solution.

Ammonium sulphate solution saturated at 32 C. was used, so that ⅛, ¼, ⅓ and ½ saturation could be obtained. With ⅕ saturation there was, after twelve hours' standing at incubator temperature, a very faint precipitate, so faint that it was collected with great difficulty and was frequently lost. When this precipitate was redissolved in saline it made a faintly milky solution. With ¼ saturation, a

considerable amount of precipitate formed, with a slight clearing effect, and when filtered and washed with ¼ ammonium sulphate and redissolved, it gave a distinctly milky solution. One-third saturation gave even more precipitation and more clearing of the fluid, and the precipitate on redissolving was very milky. At ½ saturation, more precipitate formed, and usually a perfectly clear filtrate resulted. This precipitate when redissolved gave a milky fluid of the same appearance as the original untreated fluid. Saturation with ammonium sulphate crystals completely cleared the fluid and removed all proteins.

When dried and extracted in a Soxhlet extractor, the various fractions brought down by different degrees of saturation all contained extractable fat and all gave turbid solutions. Fractional salting out was done again in the same steps, but each portion was removed as it was thrown down, making way for each succeeding step. In this manner five fractions were collected, all containing protein and all containing fat. No fraction greatly exceeded any other in fat content, but the last one—presumably serum albumin—alone contained amounts too small to be measured. The fraction at ½ saturation was more bulky than any other, and probably contained more protein. These fractions were separated by centrifuging, and quantitative determinations of protein were not attempted on account of the difficulties involved in washing free from ammonium sulphate. It was apparent that fat was precipitated by any degree of saturation that precipitates globulin, and that ½ saturation precipitates all fat. There was apparently a zone of saturation, ⅓ to ½, that produced a precipitate heavier than others. Whenever globulin came down, fat came down in direct proportion, but when the clear filtrate after ½ saturation was dried and extracted, at most only a few milligrams of fat per hundred cubic centimeters were found. In each specimen, the precipitate obtained with ½ saturation when dried and extracted contained practically the same amount as could be obtained by extracting the dried residue of the whole fluid. A clear filtrate from porcelain filters when treated by ⅕, ¼, ⅓ and ½ to full saturation gave a precipitate with each fraction roughly equivalent to those of the unfiltered.

By every method tried—diluting and salting out with sodium sulphate or ammonium sulphate—whenever a precipitate of protein was formed fat also was precipitated. No globulin body free from fat could be obtained except that salted out from a fluid previously filtered clear. This might be thought to indicate a combination, chemical or otherwise, between fat and protein, but it will be shown later that all the salting out methods used to precipitate protein will likewise precipitate fat from a suspension in pure water. Salting out, like filtration, removes the turbid substance but does not isolate it.

MUTUAL PRECIPITATION

Mutual precipitation by various substances was employed to isolate the turbid body. When kaolin was added and the fluid well shaken and allowed to settle, no clearing was noted; nor was there any on adding animal charcoal, calcium hydroxid solution or hydrated silicate of aluminum. Ferric hydroxid produced a precipitate with the first drop added, and further addition precipitated all suspended matter, leaving a clear supernatant fluid. This clear fluid when dried and extracted contained no fat. Arsenous sulphid gave no precipitation. When alkalis were added, no change was noted in the milkiness and no precipitate was formed, the fluids being always alkaline when freshly obtained and more alkaline as they became older, even though uncontaminated by bacterial growth. When acids were added, no change was seen until the neutral point was passed and a p_H of $5+$ was reached, when a flocculent precipitate formed and settled to the bottom. Stronger acid produced a heavy precipitate, amounting to a coagulum, thus clearing the fluid. The filtrate obtained by filtering through porcelain, when treated with acid to the same degree of acidity as determined by indicators placed directly in the fluid, formed no precipitate. When more acid was added, a precipitate formed, more acid being required to form the first precipitate in the filtered than in the unfiltered.

By mutual precipitation of colloids, it is shown that a colloid of positive charge, such as ferric hydroxid, will precipitate all protein and all fat; and that negatively charged colloids, such as arsenious sulphid, kaolin or charcoal, produce no change. It is also seen that, when fat is present in the system, acidulation beyond the iso-electric point of albumin and globulin causes a flocculent precipitation; but with the fat removed, acidulation beyond that point causes no precipitate or very little after considerable time. Suspended fat is known to carry a negative charge, as explained later in the section on electrolysis, and globulin and albumin carry negative charges when in an alkaline medium. In an acid medium, fat suspensions are still negative, but protein becomes positive; we then have oppositely charged particles and mutual precipitation.

It was impossible to separate the turbid substance from other colloids in suspension by any method tried, but whenever fat was precipitated, clearing resulted. Likewise, whenever clearing was obtained, fat had been precipitated.

EXTRACTION

Extraction was employed to isolate suspended fat. Shaking with ether or petroleum ether in a separatory funnel produced no clearing, and no matter how long the shaking lasted, it extracted very little fat.

Addition of acids or of alkalis produced no additional clearing, but more fat was extracted when sufficient acid was added to produce a coagulum. Never more than 30 mg. of fat per hundred cubic centimeters could be extracted by such methods, and this amount was unusual, the average being about 10 per cent. of all extractable fat. Removal of this fat had little clearing effect on the remaining fluid; on the contrary, if shaking was much prolonged and ether kept in contact with the fluid for several days, a flocculent coagulum formed, causing more milkiness than before. Petroleum ether had less coagulating effect than had sulphuric ether, but there was no clearing. Shaking with kerosene did not produce clearing; even when kerosene was allowed to run through 300 c.c. of the fluid in a serpentine extractor, at the rate of 8 liters every twenty-four hours for five weeks, no clearing could be noted.

When the fluids were vigorously shaken with ether, this became emulsified into the water of the fluid, forming a stiff semitransparent gummy mass, which prevented further agitation of the mixture and probably interfered with fat extraction. After long standing, this mixture would settle into three layers, a watery layer below, clear ether on top, and a gummy, almost transparent layer between. The watery layer was less milky than the original fluid and so was the middle layer, but when the ether was evaporated, the fluid promptly returned to its original milkiness and the gummy layer disappeared. The slight clearing effect was a result of the emulsifying of ether into a watery protein solution and not due to any fat solvent action.

By evaporating the entire fluid to dryness and powdering the residue, a constant amount of fat could be extracted in a Soxhlet apparatus. Extracting the dried precipitate from acidulation, heat coagulation or ½ saturation constantly yielded similar results. Continued extraction for seventy-two hours usually removed all extractable fat and left a dry, fine impalpable powder. The figures for fat content given in the previous paper were from the dried residue extracted seventy-two hours with sulphuric ether. This fat when extracted was found to consist largely of neutral fat and fatty acid, with traces of cholesterol and lecithin.

The powder found remaining in the extraction thimbles was not soluble in water, saline dilute acids or alkalis. When triturated with water, a turbid mixture resulted, which rapidly sedimented out. Stronger alkalis put this powder partly into a solution, from which various protein reactions could be elicited. It was hoped that a soluble residue of protein would remain after complete extraction, but the process of drying and extracting rendered most of the protein insoluble in anything but strong acids or alkalis. Proteolytic enzymes, as found in commercial pancreatin, digested this residue, so as to form a moderately clear solution.

The filtrate from porcelain filtration when shaken with ether formed a heavy gelatinous mass similar to that of the whole fluid and prolonged exposure to ether removed no fat but left considerable coagulum in the otherwise clear filtrate; so that the fluid deprived of its turbidity and shaken with ether behaves in no way differently from the original. When shaken with a mixture of equal parts ether and alcohol, three of these fluids could be completely cleared (the two others were not tried), but this procedure had to be carried out with speed and care. As an ether-alcohol mixture, unlike ether alone, was freely miscible with watery ascitic fluid, it was a better extraction fluid, but employment of an excess of alcohol or prolonged exposure to dilute alcohol coagulated protein and obscured whatever clearing effect solution of fat might bring about.

This clearing was best done in test tubes with from 5 to 7 c.c. of the fluid to be cleared. An ether and alcohol mixture was added, 1 c.c. at a time, and vigorously shaken to accomplish mixing in the shortest time possible. Very quickly another cubic centimeter of the solvent was added and the tube quickly shaken. When approximately an equal volume of solvent has been added, the mixture suddenly clears and remains clear for a few minutes. It is never brilliantly clear, for small air bubbles are included, but before the protein coagulating effect of the alcohol begins there is a space of from a few seconds to a minute or two in which the solution of suspended fat is accomplished. When an excess of alcohol is added, milkiness returns and remains. If alcohol alone be added just short of the point where it will coagulate protein and then an excess of ether, a similar clearing results.

That fat solution is accomplished by this process was proved by adding ether and alcohol in excess, thus coagulating all protein. After this, the ether and alcohol mixture was boiled off at a very low temperature. When all traces of alcohol were gone, ether alone was added to the watery suspension of coagulated protein; and after ten minutes of gentle shaking in a separatory funnel, the ether was decanted. This was replaced by another volume of fresh ether, which, after the shaking had been repeated, was decanted. These two portions of ether when combined and evaporated to dryness contained within a few milligrams of the total amount of extractable fat of the specimen.

No such clearing as is worked by ether and alcohol combined can be done with petroleum ether and alcohol, for water will not mix freely with a mixture of petroleum ether and alcohol.

In trying to "shake out" the fat from these fluids and thereby dispel milkiness, we fail to remove fat because the fat solvent is not miscible with water (the continuous phase of the suspension), and therefore our solvent does not come in contact with the fat (the disperse phase). When the fat solvent can be made to mix with water, it removes fat

but at the same time coagulates protein, thus forming a new cause for milkiness as soon as the old one is dispelled. By careful manipulation these two steps can be separated long enough to permit a clear period between the solution of fat and the coagulation of protein, and this clearing is just enough to demonstrate that the original milkiness was due to fat.

That this solvent action of ether and alcohol is explained by so simple a matter as miscibility is doubted by Sollmann. He has observed the behavior of an oil-water system, with addition of ether and then of alcohol. He saw a distinct swelling of oil droplets after the addition of ether and a fusion of these droplets after the further addition of alcohol, which indicates that the solvent enters, but that surface forces prevent fusion of the solvated particles, and further, that alcohol lowers the surface tension so that solvated globules can fuse. It was also observed under the microscope by Dr. Sollmann that, on the addition of small amounts of calcium chlorid to these fluids, the particles in suspension flocculated but did not fuse. This flocculation did not alter the gross appearance of the fluid materials, but did modify the rate and degree of ether extraction. In one instance, up to 35 per cent. fat could be shaken out, with considerable clearing. The explanation of these phenomena is simplified if we accept the generally believed theory that these fat particles are surrounded by a thin film of soap, probably a sodium soap. In this case the calcium displaces the sodium and forms a calcium soap, which is less hydrophilic and, as seen by the clumping, more easily agglutinated.

Calcium soap films would presumably be more easily passed by ether than sodium soap films and would therefore be more easily shaken out. Furthermore, it can be presumed that, with a less hydrophilic soap membrane, there would be a rise in the solubility quotient $\frac{\text{solubility ether}}{\text{solubility water}}$, resulting in easier extraction. One must also consider changes in solubility due to a modification of surface tension or surface charge when sodium soap has been displaced by calcium soap.

FREEZING

Freezing is known to "crack" emulsions, and it was employed for that purpose. It coagulated a few flakes of protein and changed the general appearance very little, but if the specimen was centrifuged vigorously, a much wider and thicker creamy pellicle was brought up than was possible before freezing. Very little clearing could be noticed by freezing and centrifuging. If a specimen is centrifuged for one hour and all pellicle removed, and the process is repeated until none forms, this specimen, on being frozen and centrifuged again after thawing, will form a quite heavy pellicle and be appreciably cleared. This change is best accomplished by a slow process of freezing. Spec-

imens of considerable volume frozen in a cooling chamber at 18 F. show more pellicle than do those frozen by carbon dioxid.

"Cracking" the emulsion of these fluids by freezing resulted in distinct but not complete clearing. This is probably accomplished by the crystallization of water with attendant crowding together of the suspensoid. When colloid ice was formed by rapid freezing or by freezing accompanied by agitation, this "cracking" effect was wanting. Freezing did not completely clear these fluids, but greatly supplemented the clearing of sedimentation.

PEPTIZATION

Peptization was employed to reduce all protein to a simpler form that should not cause turbidity. When digested by proteolytic ferments—commercial pepsin and pancreatin—these fluids were not changed in appearance. The fermentation was controlled by digestion of suspended heat-coagulated protein and by the biuret test before and after digestion. It could be shown that, although digestion had gone to the peptone stage, there was no clearing of the specimen. Heat-coagulated protein of the control was completely cleared by the same ferment in the same time. Peptization of the white fatty residue obtained by filtration was tried with hydrochloric acid and pepsin. This rendered the mixture more fluid, but did not appreciably clear it, even though a peptone biuret reaction showed that protein had been well digested. Pancreatic fermentation of the same filtrate also made this residue more fluid and cleared it somewhat, and here digestion was shown to have split up all heat-coagulable protein, yet the clearing effect was very slight. It must be remembered that this same digesting probably split some of the fat into fatty acids and contributed to clearing in that manner.

Peptization of the whole fluid or of its concentrated milky substance did not clear these fluids, but peptization of the residue in an extraction thimble left a much clearer solution.

Peptization at best is difficult to carry completely to the peptone stage with protein. In these experiments, even though peptization was fairly complete, no clearing was noted so long as suspended fat was present, but when the fat was removed by extraction or by filtration and extraction combined, peptization cleared suspensions of the fat-free protein. This is offered as evidence that the milkiness is due to fat and to no protein substance.

ELECTROLYSIS

When these fluids were viewed under a dark-field microscope in an electric field, there was migration of the suspension, principally to the positive pole, but there was no constant and uniform direction of migration. When they were placed into an electrolysis cell and exposed

to current, the dissociation of salt liberated so much hydrochloric acid and sodium hydroxid that the change in H-ion obscured any migration of the suspension. To overcome this, the fluid was dialyzed sixty hours in a Graham dialyzer, with 200 volumes of distilled water changed twice. This usually diminished the salt content so that no reaction with $AgNO_3$ could be obtained. During this process there was considerable precipitation and clumping, but, by vigorous shaking, a fine suspension could be obtained, much like the original. This was electrolyzed in cells of original design, so constructed that the substance electrolyzed was not affected by precipitation on electrodes or by precipitation from a change in H-ion, and the entire product could be removed for examination with no loss and no mixing.

In order to get a better suspension, the fluids were in some instances diluted to six volumes with water, so that sedimentation was not rapid enough to interfere with migration. At the end of the experiment, usually in twelve or twenty-four hours, the electrolytic cells were

Summarized Results of Five Experiments

	p_H	Protein-Fat Ratio Positive Cell	Protein-Fat Ratio Negative Cell
	9	155 : 100	240 : 100
	8	300 : 100	124 : 100
	7	370 : 100	212 : 100
	6	112 : 100	320 : 100
	5	115 : 100	308 : 100
Control	9	396 : 100	376 : 100

separated by taking apart the rubber connections; the cells were shaken out, and the total solids and total fat were determined by continuous extraction. This was done at a p_H of 9, 8, 7, 6, 5, and the figures given herewith are the ratios of protein to fat in the positive and negative cells, respectively. If we assume that no other solids than protein and fat remained after dialysis, the ratio of protein to fat in each cell represents the degree of transportation by the electric current. The accompanying table gives the summarized results of five experiments.

When electrolysis was done at a p_H on the alkaline side of the iso-electric point of protein, both protein and fat migrated to the positive pole, making that cell very turbid and leaving the negative clear. When it was done at a p_H near the iso-electric point or at the acid side, fat continued to migrate to the positive, but protein went to the negative and both cells continued to be turbid. However, after adjusting both cells to their original p_H of about 9, the positive cell remained turbid and the negative one became much clearer. So far as electrolysis was capable of separating suspended protein from fat, it was likewise capable of dispelling turbidity in the former and concentrating it in the latter.

DIALYSIS

Dialysis of these fluids was of no assistance in examining the turbid substance. When thin collodion sacs were used, both protein and fat dialyzed through and both sides were turbid. Thick collodion films and parchment allowed salts to dialyze out, precipitating protein and fat; and clearing resulted.

SUMMARY OF ANALYSES

Analyzed chemically, pseudochylous fluids are invariably found to be of the nature of protein-poor blood serum to which has been added a substance in no way foreign to blood serum but still causing turbidity. Emulsified fat was found in all the specimens here examined, and evidence was presented to prove that by proper methods fat can always be found.

By physical methods of analysis, such as filtration, freezing, electrolysis and sedimentation, no turbid substance could be isolated, but one could be concentrated and otherwise much restricted, and it was always found to be emulsified fat.

Microscopic examination showed oil globules wherever turbidity was concentrated, but in the main the turbid substance was so finely divided as to present colloid properties.

Physicochemical methods for the analysis of colloids, such as salting out and mutual precipitation, like purely physical methods, could not isolate but only concentrated the turbid substance, and here again it was found to be emulsified fat.

Selective solubility of proteins, as by peptization, did not dispel turbidity, but selective solubility of suspended fat, as by ether and alcohol, did dispel turbidity.

From these facts one may conclude that fat is the turbid substance. By recognizing the colloid nature of suspended fat, one is able to explain the difficulties that have prevented the acceptance of the fat theory, especially the difficulties in sedimenting, in shaking out and in salting out, for colloid fat is very different from fat in larger masses.

SYNTHESIS

In Vivo.—To prove that chyle may be the source of such minutely divided fat, milky effusions were produced in two dogs by making a thoracic duct fistula into the thorax. Five dogs were operated on, only two successfully. The operation was in two stages: By the preliminary one, the duct in the neck was tied off, and by the main one, two days later, a rib was resected and a section of the duct excised, so that a fistula was produced. The day following the operation, several hundred cubic centimeters of bloody, milky fluid were obtained, and

again each day until the fifth or sixth, when both dogs had to be killed on account of empyema and pneumothorax.

These fluids were very milky, with considerable blood and exudate. On centrifuging, many cells were thrown down, and a thin creamy layer was formed. When the cells and cream were removed, the bulk of the fluid was "pseudochylous," but with a rather high protein content. The average fat content before centrifuging was 200 mg. per hundred cubic centimeters. The averages after centrifuging were: specific gravity, 1.050; total nitrogen, 900 mg. per hundred cubic centimeters; total fat, 40 mg. per hundred cubic centimeters.

When treated by further centrifuging, by sedimentation, filtering, heat coagulation, salting out, mutual precipitation, extraction of peptization, these fluids behaved in every respect like the pseudochylous fluids tested above, so far as their milkiness was concerned. This demonstrates that chyle can be the source for finely suspended fat such as is seen in pseudochylous fluids.

In Vitro.—To synthesize fluids as accurately as possible, it is necessary to obtain a very finely divided suspension of oil, which may be added to perfectly clear ascitic fluid until the natural fluids are matched as to milkiness. The first attempt to secure such a synthetic fluid was made by dissolving cod liver oil in ether, 1.5 gm. to 90 c.c. This ether-oil solution was floated on the top of 1 liter of distilled water in a mixing cylinder and very vigorously shaken. This much ether mixes readily with a liter of water, leaving the oil finely divided and suspended. The suspension even with vigorous shaking is not permanent, and if not further treated soon settles out as a cream. Before settling took place, the mixture was twice run through an homogenizer at about 800 pounds' pressure. The homogenizer was of the Manton-Gaulin type, in which coarse oil suspensions are forced through the very narrow slit between a valve and a valve seat. Powerful electric pumps force the droplets through by breaking them into fragments. Before being homogenized, the suspension was scarcely turbid, but after homogenization it was very milky. Air was then bubbled through for several hours, and all traces of ether removed. After a week or more, a cream came up, and the milkiness was somewhat diminished. The underlying fluid was siphoned out, and remained unchanged several months. This fluid added to clear ascitic fluid made a good "pseudochylous" ascitic fluid. It contained about 50 mg. of fat per hundred cubic centimeters, and 300 mg. of protein.

A second water suspension was made with liquid petrolatum, but this mixture was not very stable and continued to form a cream, so that, after two months, there were in suspension but 5 mg. of oil per hundred cubic centimeters, although the mixture was still quite milky in appearance. A third suspension was made from fat extracted from

natural ascitic fluid, simple shaking being relied on, without homogenization, which requires very large volumes on account of the capacity of the machine. This suspension was stable at 100 mg. per hundred cubic centimeters, and was very milky.

All three synthesized fluids resembled the natural very closely in gross appearance, but microscopically the fat particles were very much larger, and the addition of protein did not alter their size, arrangement or brownian movement. When these fluids were tested by the methods used on the natural fluids, very few differences were noted, and none of them were in essentials. Filtering through paper removed nothing from any specimen except from the one made with mineral oil. In this one, the fat particles were largest, but filtering through porcelain removed all fat. Sedimentation except in the mineral oil system removed nothing either up or down, but heat coagulation with weak acids completely cleared them all. Salting out showed the same clearing effects as in the natural fluids; whenever any globulin was precipitated, fat was also precipitated, and clearing resulted. Mutual precipitation reactions were also the same as in the natural fluids; fat was precipitated by any colloid bearing a positive charge, and whenever globulin was precipitated, fat was likewise precipitated. As in the natural fluids, very slight acidulation, just sufficient to go beyond the iso-electric point of serum albumin, gave marked flocculation but not complete clearing. Extraction gave the same results as before, but simple shaking with ether partly cleared the mineral oil system. Shaking with ether removed no fat from the cod liver oil system, but ether and alcohol cleared it promptly. Freezing partly cleared all three systems by precipitating protein and causing cream to come up. Peptization partly cleared both the cod liver oil and the natural human fat systems, but did not affect the mineral oil system. Electrolysis showed a concentration of fat always to the positive pole, and in an alkaline medium a concentration of protein to the negative; but it never accomplished a complete separation.

To summarize the results of examining these synthetic fluids, it must be said that they differ from the natural only in minor points, and the difference can be largely accounted for by poor homogenization; for no artificial means tried here could break up oils and fats into such small particles as naturally occur. In synthetic fluids, fat alone can cause milkiness.

In order to determine what rôle fat alone might play in determining the physical characteristics of milky fluids, simple oil-water systems of cod liver oil, mineral oil and human fat, made as described above, except that no ascitic fluid or other protein was added, were examined, with the following results:

Milkiness, as determined by reading print through tubes, was quite marked with as low as 20 mg. per hundred cubic centimeters, but a

natural fluid containing this amount was more turbid. No oil could be made to pass a porcelain filter, and as much as 80 mg. per hundred cubic centimeters of cod liver oil suspension would stand centrifuging indefinitely without settling out. Peptization and heating to the boiling point with acid had no effect, there being no protein present. Salting out with ammonium sulphate at one-half saturation always cleared all three systems, and salting to less than one-half saturation would clump up the particles to form a watery layer on top. Salting with saturated sodium chlorid in the presence of acid cleared them completely, as did mutual precipitation with any positively charged colloid, if used in proper amount, as determined by trial. Extraction by shaking with ether, even when long continued, did not clear any but the mineral oil systems and then not completely, but shaking with ether and alcohol mixture cleared them all three completely and instantly. Freezing when done gradually cleared them; but if it was done rapidly, especially if the tubes were agitated while freezing, the clearing was not complete. Electrolysis always caused these suspensions to migrate completely to the positive pole in acid or alkaline mediums.

From these results, it can be seen that suspended fat, even when not very finely divided, can account for milkiness that will not filter out with paper, will not settle out by gravity and will not shake out with ether alone, but will salt out; and these were the principal arguments whereby turbidity was ascribed to protein and the term pseudochylous came to be introduced.

ADSORPTION OF PROTEIN

Although it is not essential to an investigation into the milkiness of these fluids, it is interesting to speculate what relation there may be between fat and protein in either the natural fluids or the synthetic. When fats and protein are both in an alkaline medium and hence freely suspended, there may be no relation other than that of two separate dispersoids in the same continuous phase. The great difficulty found in separating them may be due altogether to the similarity of their properties as colloids in suspension.

When the two substances are collected together from their watery medium, they are never found in constant ratios, as can be seen by making total nitrogen determinations on measured amounts of precipitate removed by filtration, heat coagulation, salting out or electrolysis. This militates against any chemical union of the two substances.

The physical relation of adsorption must be considered, for it is a property common to colloids in suspension to adsorb substances. Adsorption probably takes place when acidulation or heat coagulation removes both these substances from suspension, but then we have altered

the protein by reversing the electric charge from negative to positive, while the fat remains unchanged. A fusion in the nature of adsorption then occurs between particles.

In the synthesized milky fluids that remain stable, there was no adsorption demonstrable. This was tested by two experiments:

Protein was added to a supersaturated oil-water system before any oil had settled out. After twenty-four hours, when a heavy cream had come to the top, the cylinder, which was 15 cm. long and held 100 c.c., was pipetted into two halves, an upper and a lower, and a nitrogen determination was made on equal amounts of top and bottom, discarding, by way of precaution against protein sedimentation, the very bottom 2 or 3 c.c. The total amounts of nitrogen on top and on bottom were almost equal, showing no concentration of protein at the top. By this process of "flotation," it was expected that protein, if adsorbed to fat particles, would be concentrated at the top with the fat; but there was no concentration.

The problem was approached from another angle by adding protein to a watery suspension of cod liver oil that had been deprived of all cream by settling and siphoning, and had been homogeneous for a long time. This procedure determined the maximum size at which fat particles could stay free in suspension. Blood serum was then added, the protein in which was free to be adsorbed to the fat particles and thereby augment their size above the maximum, so that a cream should develop. After a week, no cream had come up, nor was the turbidity increased.

While neither of the foregoing is a critical experiment, they are cited as evidence against adsorption of protein to fat. Whether any substances other than protein may be adsorbed to fat particles need not be considered in this investigation, but there is a possibility of soap in this rôle. While no soap could be discovered, it may still be present in quantities sufficient to form a surface film over particles of fat. This is suggested by the fact that mineral oil, which cannot saponify when suspended in pure water, made a much less stable system than did cod liver oil or human fats, both of which may be saponified by the alkali present in the serum; and it is further suggested by the phenomenon seen on the addition of calcium and noted above under extraction.

SUMMARY AND CONCLUSIONS

Five so-called pseudochylous fluids examined chemically were found to be protein-poor blood serum made turbid by some unknown substance. This substance was found by selective solubility, partial isolation, concentration and other restriction to be emulsified fat, so finely divided that it had assumed properties common to colloids.

By operating on the thoracic duct, dogs were made to develop pseudochylous fluids from chyle.

Pseudochylous fluids were synthesized from oil-water mixtures.

By recognizing the colloid properties of suspended fat, we discover the fallacies whereby the term pseudochylous originated. The term pseudochylous is misleading and should be discarded.